Efficacy and Safety of Botulinum Neurotoxin NT 201 in Poststroke Upper Limb Spasticity

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Objective: To assess the impact of the new botulinum neurotoxin type A preparation NT 201 (Xeomin®; Merz Pharmaceuticals GmbH, Frankfurt, Germany) on muscle tone, functional disability, and caregiver burden in patients with poststroke upper limb spasticity in a randomized, placebo-controlled, double-blind study.

Methods: One hundred forty-eight patients with an Ashworth Scale score of 2 or higher for wrist and finger flexors and at least moderate disability in their principal therapeutic target of the Disability Assessment Scale were treated either with NT 201 (median, 320 U) or placebo and followed up for up to 20 weeks. Treatment of the wrist and finger muscles was mandatory.

Results: A significantly higher proportion of patients treated with NT 201 were responders (improvement of ≥1 point in the Ashworth Scale score), as observed in comparison to placebo 4 weeks after treatment in wrist flexors (odds ratio, 3.97; 95% confidence interval, 1.9–8.3; $P < 0.001$, intent to treat). For all treated flexor muscle groups, statistically significant odds ratios in favor of NT 201 were observed at week 4 ($P \leq 0.009$). Statistically significant results in favor of NT 201 were observed at all postinjection visits until week 12 in the principal therapeutic target ($P \leq 0.005$), in the global assessment of efficacy ($P < 0.001$), and in some tasks of the Carer Burden Scale ($P < 0.05$). Similar numbers of patients in each group experienced at least 1 adverse event (NT 201, n = 21; placebo, n = 20). Importantly, none of the patients developed neutralizing antibodies.

Conclusions: NT 201 led to statistically significant improvements in muscle tone and disability and was well tolerated in patients with poststroke upper limb spasticity.

Key Words: botulinum toxin type A, NT 201, stroke, upper limb spasticity

(*Clin Neuropharm* 2009;00: 00–00)

Spasticity has been defined as a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as 1 component of the upper motor neuron syndrome.[1] Prevalence 1 year after first-ever stroke is 17% for any spasticity and 4% for disabling spasticity.[2] Poststroke muscle spasticity frequently impacts on activities of daily living, personal hygiene, and ambulation and can cause pain and significant discomfort.[3,4]

Pharmacological treatment options include systemic antispastic medication or treatment by chemodenervation using alcohol or botulinum neurotoxin type A (BoNT/A). Owing to a local antispastic effect, treatment with BoNT/A is considered to have major advantages in the treatment of focal spasticity, when compared with systemic antispastic drugs, which are nonselective in their action and may weaken unaffected muscles. The use of oral antispastic medication is further limited by adverse effects, which include hypotension, drowsiness, diarrhea, nausea and vomiting, hepatotoxicity, confusion, and sedation. Treatment with sedating antispastic medications in patients with stroke is associated with specific concerns because of poor tolerance by patients with cognitive impairment.[5] A comparison of BoNT/A and tizanidine recently demonstrated better safety and efficacy outcomes for botulinum neurotoxin.[6] Two recent evidence-based reviews found BoNT/A as an effective and safe medication in spasticity management and recommend its use for upper and lower limb spasticity after stroke.[7,8]

NT 201 (Xeomin; Merz Pharmaceuticals GmbH, Frankfurt, Germany) is a highly purified, freeze-dried BoNT/A formulation free from complexing proteins. In contrast to 2 other BoNT/A formulations, NT 201 did not induce the formation of BoNT/A-neutralizing antibodies in an animal model.[9] This might provide therapeutic advantages; particularly in indications that necessitate higher total doses and long-term therapy. NT 201 showed comparable treatment efficacy and tolerability to a different BoNT/A formulation (Botox®; Allergan Inc., Irvine, CA) in two phase 3 clinical studies for focal dystonia (cervical dystonia[10] and blepharospasm[11]).

The present placebo-controlled study assessed the efficacy and safety of 1 set of intramuscular NT 201 injections in the treatment of poststroke upper limb spasticity.

MATERIALS AND METHODS

This randomized, double-blind, placebo-controlled phase 3 study was carried out at 23 sites in 3 European countries (Czech Republic, Hungary, and Poland) from June 2006 to January 2007 (trial registered at ClinicalTrials.gov Id, NCT00465738) and was conducted according to the Good Clinical Practice and the Declaration of Helsinki. The study protocol was approved by the ethics committees responsible for each participating site, and written informed consent was obtained from all participating patients before any study-related procedure took place.

Adult patients with a history of stroke (at least 6 months before enrollment) resulting in focal spasticity of wrist and finger flexors (as demonstrated by the presence of the respective clinical patterns and a score of ≥2 on the Ashworth Scale[12])

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I.S., G.C., and S.G. are employees of Merz Pharmaceuticals GmbH, Frankfurt, Germany.

This study was supported by Merz Pharmaceuticals GmbH, Frankfurt, Germany. The editorial assistance was also paid by the company.

DOI: 10.1097/WNF.0b013e3181b13308

were eligible for inclusion. A score of 2 or higher (moderate) on the Disability Assessment Scale (DAS) in 1 of 4 domains chosen as the principal therapeutic target[13] was also required. Antispastic medication with centrally acting muscle relaxants and/or benzodiazepine medication and physical and occupational therapy regimens were permitted if they had been stable in the 2 weeks before screening; no treatment changes were allowed during the study. Physical and occupational therapies were, however, not allowed on study visit days before outcome assessments to avoid any impact on spasticity evaluations. Main exclusion criteria were spasticity of any other origin than stroke, bilateral upper limb paresis, botulinum toxin treatment within the last 4 months, previous or planned treatment with phenol or alcohol injection or surgery in the target limb, fixed contracture, other muscle hypertonia, neuromuscular disorders such as Lambert-Eaton syndrome, myasthenia gravis, or amyotrophic lateral sclerosis, current treatment with intrathecal baclofen, severe atrophy of the target muscles, and hypersensitivity to the study medication. Female subjects of childbearing potential were excluded if they were without adequate contraception, pregnant, or lactating.

Treatment

After a 1-week screening period, patients were randomly assigned to either NT 201 or placebo by a computer-generated list stratified by the centers. Patients were administered a single set of intramuscular injections for their upper limb spasticity during baseline visit. The appropriate localization of the needle in the muscle targeted for treatment was assured by means of electrical stimulation or recording of electromyographic signal (EMG). Appearances and solution properties of NT 201 and placebo were identical. Because previous preclinical and clinical studies indicated a dose ratio of 1:1 for NT 201 to another BoNT/A formulation (Botox®),[14] treatment of the affected muscles was based on starting dose recommendations for this formulation as published by the WE MOVE organization.[15]

The maximum intended dose of study medication was 400 U. Each muscle for the clinical patterns flexed wrist and clenched fist had to be treated. Other spastic upper limb muscle groups were treated as individually needed. Flexors of elbow and thumb as well as forearm pronators had to be treated only in the presence of a corresponding clinical pattern (flexed elbow, thumb-in-palm, and pronated forearm) and if the Ashworth Scale score in that muscle group was at least 2. The choice of muscle to be treated within the muscle groups of forearm pronators and thumb flexors was based on the investigator's clinical judgment. In the group of elbow flexors, treatment of biceps and at least 1 additional muscle was mandatory. In case of a lower Ashworth Scale score with present corresponding clinical pattern, treatment was at the investigator's discretion. If all listed muscle groups showed a clinical pattern and an Ashworth Scale score of 2 or higher, the investigator decided which muscles within a muscle group had priority for treatment, to not exceed the maximum dose of 400 U.

Mandatory assessment visits were performed 2, 4, 8, and 12 weeks after injection (baseline visit). After 12 weeks, an optional phase until 20 weeks was possible if there was no need for a new injection.

Efficacy Assessment

Ashworth Scale

Investigators assessed the tone of the wrist, finger, elbow, and thumb flexors and forearm pronators at each visit using the 5-point Ashworth Scale ranging from 0 (no increase in tone) to 4 (limb rigid in flexion or extension).[12] A reduction by 1 point is considered clinically meaningful.[16,17] A pretrial training session was conducted, and a standardized method for assessments on the Ashworth Scale was used.[18]

Disability Assessment Scale

Functional disability was rated at each visit by the investigators and the patient on the 4-point DAS (0, no disability; 3, severe disability) consisting of the 4 domains: hygiene, dressing, limb position, and pain. Good interrater and intrarater reliability of the Ashworth Scale and DAS and a good correlation between the scores of these scales have been previously demonstrated.[13,17] Before the start of treatment, each patient (in consultation with the investigator) selected 1 of the 4 disability domains as the principal therapeutic target.

Carer Burden Scale

The Carer Burden Scale measures the impact of upper limb spasticity on the physical carer burden.[19] Items include cleaning the palm of the affected hand, cutting the fingernails of the affected hand, cleaning the armpit of the affected arm, and putting the affected arm through a sleeve. We additionally included applying a splint to the affected arm because it is known that this activity is often troublesome for carers. Difficulty of the task was rated from 0 (no difficulty) to 4 (cannot do the task) by the caregivers at baseline and at week 4, 12, and final visit.

Global Assessment of Treatment Benefit

Overall treatment benefit (ranging from 1 [very good] to 4 [poor]) was evaluated by investigators, patients, and caregivers at the final visit.

Time to Onset of Effect and Time to Waning of Effect

Time of onset of effect and time of waning of effect were assessed based on the patients' subjective estimation.

Safety

Safety was assessed throughout the study by adverse event (AE) monitoring, vital signs, and standard clinical and hematological laboratory testing. An electrocardiogram was performed at screening. Predefined AEs of special interest included dyspnea, respiratory tract infections, dry mouth, dysphagia, speech problems, facial weakness, and general body weakness, as well as all other signs and symptoms, which the investigator considered to indicate toxin spread. In addition, investigators were asked to rate the patients' overall treatment tolerability (from 1 [very good] to 4 [poor]) at the final visit.

Blood samples collected at screening, week 4, and the final visit were screened for botulinum toxin antibodies using a fluorescence immunoassay in a microplate format. Positive samples were subsequently tested using the mouse hemidiaphragm assay (HDA) for neutralizing antibodies.[20]

Statistical Analysis

All statistical analyses were performed with SAS version 8.2 (SAS Institute, Cary, NC). Efficacy was analyzed using the intent-to-treat (ITT) population, which included all randomized patients. The primary efficacy parameter was the response rate for the wrist flexor treatment at week 4. Responders were defined as patients with a 1-point or higher improvement (reduction) from baseline in the Ashworth Scale score. The probability of being a responder in the NT 201 treatment group was compared with the probability of being a responder in the placebo treatment group (odds ratio $[OR]_{NT\ 201/placebo}$). The null hypothesis was equality of the chance (ie, OR, 1) for a clinically relevant

TABLE 1. Baseline Characteristics of the Intention-to-Treat Population

	NT 201 (n = 73)	Placebo (n = 75)	Total (n = 148)
Male/female, %	62/38	67/33	64/36
Mean (SD) age, yr	58.1 (10.2)	53.3 (13.3)	55.6 (12.1)
Mean (SD) BMI, kg/m^2	26.4 (4.6)	26.3 (3.5)	26.3 (4.1)
Mean (SD) time since first diagnosis of spasticity, mo	60.9 (49.1)	49.2 (47.9)	55.0 (48.7)
Patients pretreated with BTX-A, n (%)	21 (28.8)	15 (20)	36 (24.3)
Treatment-naïve, n (%)	52 (71.2)	60 (80)	112 (75.7)

BTX-A indicates BoNT preparations other than NT 201.

treatment effect in the 2 treatment groups. A logistic regression model was used to compare treatment groups for the Ashworth Scale score on baseline, sex, age, body mass index (BMI), pretreated/naive patients, and pooled centers as covariates.

Odds ratios were also calculated for Ashworth Scale scores involving all 5 upper limb muscle groups at weeks 2, 4, 8, 12, and final visit. All other efficacy parameters were analyzed descriptively. Missing data for all secondary efficacy parameters were carried forward as zero change. For treatment comparison, Wilcoxon and Mann-Whitney *U* tests were performed. Differences were considered significant at $P < 0.05$. The relationship between different scales was assessed by Spearman rank correlation coefficient.

Sample size calculation was based on expected response rates for patients with a clinically meaningful improvement from baseline of 1 or higher on the Ashworth Scale.[16,17] A 3.5-fold higher chance (OR) of an effect in the NT 201 group relative to placebo was assumed. A 2-group continuity corrected χ^2 test with a 2-sided significance level of $\alpha = 0.05$ would have 90% power to detect an OR of 3.5 if the sample size in each treatment group were 63. Assuming a 10% rate of invalid and/or missing data, it was calculated that 70 patients per treatment group were needed for randomization.

All randomized patients receiving the study medication were included in the safety analysis. Safety data were analyzed descriptively. Adverse events were coded according to MedDRA, Chantilly, VA, version 9.1.

RESULTS

A total of 148 patients were randomized (NT 201, n = 73; placebo, n = 75). All patients were included in ITT and safety analyses. Three patients prematurely discontinued the study; 1 in the placebo group (death due to intracranial hematoma) and 2 in the NT 201 group (withdrawn consent, 1; AE [paraparesis], 1). Baseline characteristics of the 2 treatment groups were similar (ITT population; Table 1). NT 201 patients were slightly older and had suffered from stroke-induced spasticity almost a year longer than their placebo counterparts. Most patients (75.7%) had never been treated with botulinum toxin for upper limb spasticity and were defined as treatment-naive. Pretreated patients (24.3%) had received a mean of 3.4 (SD, 2.9) BoNT injection sessions since first diagnosis. The median time since the most recent treatment was 7 months (range, 3.9–77.2 months); the 2 administered preparations were Dysport® (14.2%) and Botox® (10.1%). The finger and wrist flexors were the most commonly treated muscle groups.

In addition to the clinical patterns, flexed wrist, and clenched fist (inclusion criteria), most patients (91.9%) presented with upper limb spasticity in other muscle groups. Table 2 shows the different combinations of clinical patterns in the study population; the variety of which closely mirrors the clinical practice situation.

The median NT 201 dose administered was 320 U (mean, 307 U; range, 80–435 U, minimum and maximum units, respectively). One patient treated with placebo and 1 patient treated with NT 201 (435 U) received a marginally higher than

TABLE 2. Mean (SD) Doses Administered to Individual Muscles of the 5 Clinical Patterns

Clinical Pattern	NT 201	Placebo*	Total
Muscle Treated		**U**	
Total dose for flexed wrist	90 (0)	90 (0)	90 (0)
Flexor carpi radialis	50 (0)	50 (0)	50 (0)
Flexor carpi ulnaris	40 (0)	40 (0)	40 (0)
Total dose for clenched fist	80 (0)	80 (0)	80 (0)
Flexor digitorum superficialis	40 (0)	40 (0)	40 (0)
Flexor digitorum profundus	40 (0)	40 (0)	40 (0)
Total dose for flexed elbow	142.4 (30.2)	143 (33.7)	142.7 (31.9)
Brachioradialis	59.7 (1.7)	59.7 (1.8)	59.7 (1.7)
Biceps	80 (0)	80 (0)	80 (0)
Brachialis	50 (0)	49.5 (2.6)	49.8 (1.9)
Total dose for pronated forearm	47 (15.9)	47.5 (15.2)	47.3 (15.5)
Pronator quadratus	25 (0)	25 (0)	25 (0)
Pronator teres	40 (0)	40 (0)	40 (0)
Total dose for thumb-in-palm	25.4 (10.3)	24 (8)	24.6 (9.1)
Flexor pollicis longus	20 (0)	19.8 (1.0)	19.9 (0.7)
Adductor pollicis	10 (0)	10 (0)	10 (0)
Flexor pollicis brevis/opponens	10 (0)	10 (0)	10 (0)

*The number of units of placebo corresponds to the number of units of NT 201 the patient would have received if they had been randomized to the NT 201 group.

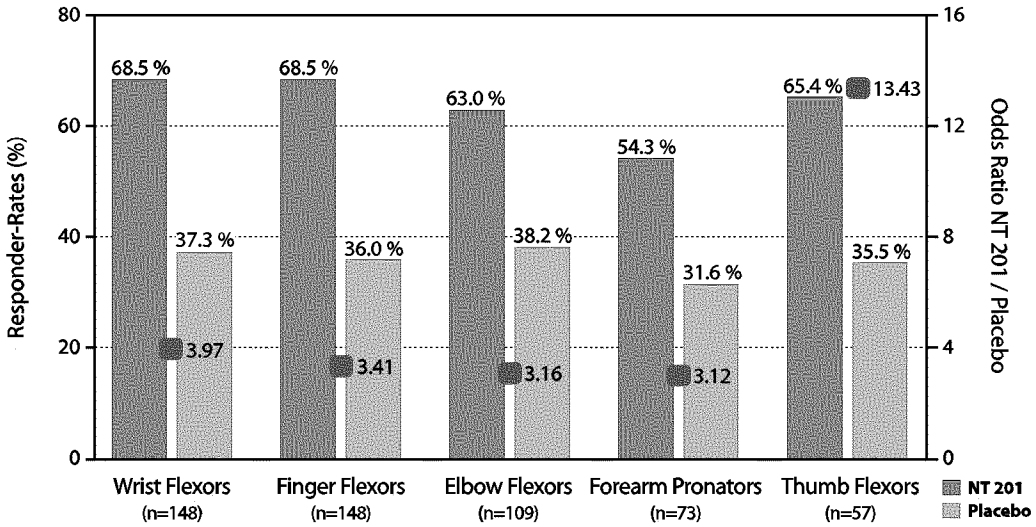

FIGURE 1. Responder rates (a treatment response was defined as ≥1-point improvement on the Ashworth Scale) for all treated muscle groups at week 4 (ITT population).

TABLE 3. Proportion of Responders to Treatment of Different Muscle Groups (≥1-Point Improvement in the Ashworth Scale Score) at All Visits After Injection (ITT Population)

	% Response		$OR_{NT\ 201/Placebo}$	
	NT 201	Placebo	(95% CI)	*P*
Flexed wrist	n = 73	n = 73		
Week 2	61.6	30.1	4.22 (1.98–8.99)	<0.001
Week 4	68.5	37.3	3.97 (1.90–8.30)	<0.001
Week 8	67.1	30.1	5.55 (2.55–12.09)	<0.001
Week 12	42.5	24.7	2.61 (1.12–6.05)	0.026
Final Visit	39.7	19.2	3.64 (1.41–9.40)	0.007
Clenched fist	n = 73	n = 75		
Week 2	68.5	29.3	5.31 (2.46–11.44)	<0.001
Week 4	68.5	36.0	3.41 (1.62–7.20)	0.001
Week 8	60.3	36.0	2.68 (1.29–5.55)	0.008
Week 12	47.9	30.7	2.00 (0.92–4.34)	0.079
Final visit	38.4	22.7	1.86 (0.84–4.14)	0.128
Thumb-in-palm	n = 26	n = 31		
Week 2	61.5	25.8	16.50 (2.77–98.33)	0.002
Week 4	65.4	35.5	13.43 (2.28–78.99)	0.004
Week 8	53.8	45.2	3.31 (0.71–15.43)	0.128
Week 12	53.8	32.3	11.87 (1.60–87.85)	0.015
Final visit	42.3	32.3	2.56 (0.44–14.85)	0.294
Flexed elbow	n = 54	n = 55		
Week 2	59.3	27.3	4.42 (1.80–10.85)	0.001
Week 4	63.0	38.2	3.16 (1.33–7.51)	0.009
Week 8	50.0	40.0	1.52 (0.66–3.52)	0.323
Week 12	42.6	29.1	1.81 (0.69–4.73)	0.225
Final visit	38.9	25.5	1.97 (0.75–5.18)	0.169
Pronated forearm	n = 35	n = 38		
Week 2	45.7	26.3	3.62 (0.99–13.17)	0.051
Week 4	54.3	31.6	3.12 (0.97–10.07)	0.057
Week 8	51.4	28.9	3.25 (1.01–10.48)	0.048
Week 12	34.3	28.9	2.45 (0.65–9.25)	0.185
Final visit	28.6	26.3	1.81 (0.46–7.04)	0.394

CI indicates confidence interval; n, number of patients in which the corresponding muscle group was treated.

the maximum recommended dose of 400 U. Table 2 lists the mean administered doses for individual muscles. Doses were similar for both treatment groups.

Efficacy

Ashworth Scale

A larger proportion of NT 201 patients were rated responsive to treatment (≥1 point reduction in the Ashworth Scale score) in all 5–treated muscle groups at week 4 compared with placebo patients (Fig. 1). A significant and clinically meaningful OR of 3.97 (95% confidence interval, 1.9–8.3; $P < 0.001$) in favor of NT 201 was observed for the primary variable wrist flexor treatment. There were no significant effects of any of the covariates (Ashworth Scale score on baseline, sex, age, BMI, pretreated/naive patients, and pooled centers) included in the logistic regression model. Significant ORs in favor of NT 201 ranging from 3.16 to 13.43 ($P < 0.009$) were also observed for all other flexor muscle groups at week 4 (Fig. 1, ITT population).

Table 3 summarizes the treatment response on muscle tone for all 5 upper limb clinical patterns at all assessment visits. Overall, markedly more NT 201 patients experienced improvements at all postbaseline visits compared with placebo. After 8 weeks of treatment, at least 50% of NT 201 patients were still responders in all muscle groups.

Disability Assessment Scale

Sixty patients (40.5%) chose dressing, 54 patients (36.5%) limb position, 30 patients (20.3%) hygiene, and 5 patients (3.4%) pain as principal therapeutic target.

The treatment groups were homogeneous about the number of patients choosing the same domain. Improvements from baseline in the principal therapeutic target were observed at weeks 2, 4, 8, and 12 with significant differences in favor of NT 201 ($P \leq 0.005$). In addition to the significant change in the domain chosen as principle therapeutic target, significant superiority over placebo was also observed in each individual's DAS domain. Statistically significant superiorities of NT 201 versus placebo in individual DAS domains were as follows: hygiene (weeks 2, 4, and 8; $P \leq 0.05$), dressing (week 2; $P = 0.003$); limb position (weeks 2, 4, and 8; $P \leq 0.009$); and pain (weeks 2 and 4; $P \leq 0.042$).

Carer Burden Scale

Superiority of NT 201 over placebo was observed for the items putting the affected arm through a sleeve ($P = 0.021$) and for cleaning the palm of affected hand ($P = 0.028$; ITT population) at week 4.

Global Assessment of Treatment Benefit

Treatment benefit was rated significantly better for NT 201 than placebo by investigators ($P < 0.001$), patients ($P < 0.001$), and caregivers ($P = 0.001$). Figure 2 shows the ratings by all 3 groups. Nineteen placebo (25.3%) and 26 NT 201 patients (35.6%) did not have a carer or did not participate in the carer rating.

Time to Onset of Effect and Time to Waning of Effect

The median time of onset of effect as reported by patients was 4 days for the NT 201 injection; the median time reported for a waning of the treatment effect was 10 weeks.

Correlations

There was a correlation of the mean change in the Ashworth Scale score (all clinical patterns treated) at week 4 with the change in the principle therapeutic target of the DAS scale ($r = 0.44$; $P < 0.0001$). The correlation of the Patient's Global Assessment of treatment benefit was calculated with the mean change in the Ashworth Scale score of all clinical patterns treated. There was a statistically significant correlation of these parameters, with the Spearman rank correlation coefficient $r = 0.60$ and $P < 0.0001$.

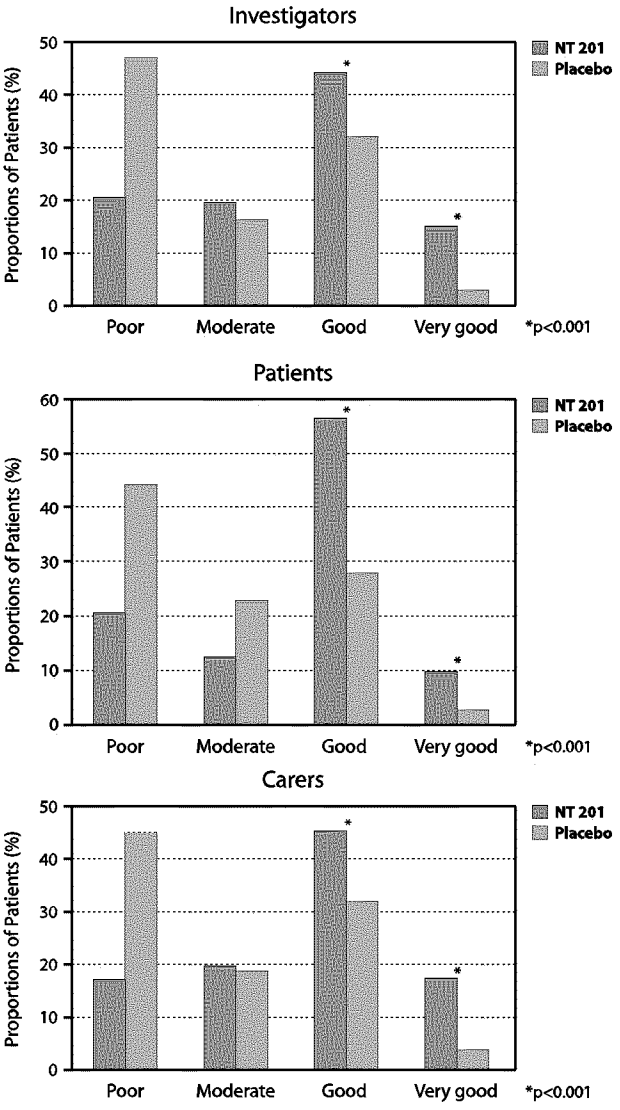

FIGURE 2. Global assessment of treatment benefit by investigators, patients, and caregivers (Wilcoxon 2-sample test, ITT population).

Safety

Adverse events were documented for 21 patients (28.8%) in the NT 201 and 20 patients (26.7%) in the placebo group; most were mild in intensity. The majority (71%) had resolved/recovered at the final visit. One patient in the placebo group died because of an intracranial hematoma. Table 4 lists all AEs occurring in at least 2% of patients in 1 treatment group, regardless of causal relationship. Incidences were similar between the groups. Five patients (2 patients treated with NT 201, 3 placebo patients) experienced a total of 12 treatment-related AEs. These were feeling hot (4 events), headache (3), and 1

TABLE 4. Adverse Events Occurring in at Least 2% of Patients in 1 Treatment Group Regardless of Causal Relationship*

	NT 201 (n = 73)	Placebo (n = 75)	Total (n = 148)
Diarrhea	2 (2.7)	2 (2.7)	4 (2.7)
Headache	2 (2.7)	1 (1.3)	3 (2.0)
Hyperglycemia	3 (4.1)	0	3 (2.0)
Contusion	1 (1.4)	2 (2.7)	3 (2.0)
Hypercholesterolemia	2 (2.7)	1 (1.3)	3 (2.0)
Epilepsy†	2 (2.7)	0	2 (1.4)
Vomiting	0	2 (2.7)	2 (1.4)

Data are number of patients (%).

*The event considered drug related was headache in 1 NT 201 patient.

†Adverse event occurred in patients with known epilepsy reported as concomitant disease.

event of dysesthesia, hypoesthesia, dysphagia, injection site pain, and injection site hematoma. Adverse events of special interest were observed in 1 patient in the NT 201 group (nasopharyngitis) and in 4 patients in the placebo group (dysphagia, rhinitis, pharyngitis, influenza, and respiratory tract infection). Only dysphagia in the placebo group was considered treatment related.

No major treatment differences were found regarding abnormal laboratory variables, vital signs, and physical and neurological examinations.

Investigators rated treatment tolerability as "good" or "very good" in 96.7% of all patients with no major differences between NT 201 and placebo treatment groups ($P = 0.77$).

Neutralizing Antibodies

Most of the patients (95.3%) had a negative fluorescence immunoassay assessment. Subsequent testing of positives with the HDA assay did not detect neutralizing antibodies against the study medication in any patient.

DISCUSSION

In this randomized, double-blind study, a single set of NT 201 injections into spastic upper limb muscles proved to be significantly more efficacious than placebo for patients with poststroke upper limb spasticity. During the entire treatment period, the proportion of treatment responders with improved muscle tone was consistently higher in the NT 201 group compared with placebo for all 5–treated muscle groups (flexors of the wrist, finger, elbow, and thumb as well as forearm pronators). Statistical significance in all upper limb flexor muscle groups and high ORs in all muscle groups treated were observed at week 4. These results clearly favor the treatment with NT 201 compared with placebo.

In previous double-blind, placebo-controlled studies with other BoNT/A formulations, a significant superiority over placebo was most commonly reported for wrist flexors.[6,17,21–25] Finger flexor treatment was significantly more effective than placebo in some studies[6,17,19,22,24] but the effect was less consistent at different time points and with different doses in other studies.[23,25] For other BoNT/A preparations, significant superiority of BoNT/A treatment was reported for muscle tone reduction in elbow flexors in several studies[19,21,23,25] but did not reach significance in all studies.[22,24] One study reported no tone reduction differences between BoNT/A and placebo in elbow flexors and pronators.[6] It is surprising that spasticity of thumb flexors was not treated in most placebo-controlled studies with botulinum toxin, since thumb is essential to the hand's function. In the present study, the increased muscle tone in thumb flexors was effectively treated with NT 201. Effective treatment of spasticity in thumb flexors was also shown in 1 previous double-blind trial with BoNT/A.[17]

Reduction in muscle tone is closely related to the pharmacological effect of BoNT/A, which is well known. Clinical evaluations of changes in muscle tone were based on Ashworth Scale score assessments in this study. Although this scale has often been criticized because of some limitations, it is a widely accepted scale for the clinical assessment of spasticity. Standardization of Ashworth Scale score assessments seems to be essential, especially in a multicenter clinical trial. Therefore, a standardized approach for both test administration and scoring, as described by Platz et al,[18] was used for Ashworth Scale score assessments in this clinical trial. The use of these standardized guidelines was shown to assure comparability of test administration and scoring across raters and time.[18]

The assessment of a relationship between the mean Ashworth Scale score change from baseline for all 5–treated muscle groups and changes in the DAS score for principal therapeutic target demonstrated significant correlations between both scales. Global treatment benefit assessment by patients was also found to be significantly correlated to the Ashworth Scale, indicating the relevance of the change on the Ashworth Scale for patients.

The present study is, to our knowledge, the first placebo-controlled study with BoNT/A to include these 4 flexor muscle groups and additionally, forearm pronators in the treatment regimen. A broad spectrum of upper limb muscles was considered for the treatment, allowing physicians to be flexible when making a decision as to which muscles should be treated from the clinical point of view. Although some degree of standardization was given by the included patient population (ie, mandatory presence of spasticity in the wrist and fingers), in this study clinical practice is closely mirrored by taking into account the heterogeneity of the clinical picture of upper limb spasticity. Based on this heterogeneity, muscle groups of elbow and thumb flexors as well as forearm pronators could have been optionally treated, when clinically indicated. Indeed, 91.9% of the patients had other upper limb muscle groups affected by spasticity besides wrist and finger flexors. We believe that this approach significantly contributed to the overall trial results, especially with respect to consistency of improvements seen in muscle tone reduction, patients' disability, carers' burden, and overall assessment of treatment benefit.

Demonstration of functional improvements in poststroke spasticity patients with BoNT/A treatment has been associated with some difficulties in the past. This seems to be influenced by several factors, with the lack of appropriate scales being probably the most important one. Most available scales are not specific enough to detect changes occurring after a local treatment with botulinum neurotoxin. For upper limb poststroke spasticity, introduction of the DAS opened new perspectives in the evaluation of botulinum toxin treatment effects in these patients. Patients treated with NT 201 improved in a domain chosen to be their principle therapeutic target, and the effect was statistically significantly superior to placebo during 12 weeks after the treatment. This is consistent with results already observed for another BoNT/A preparation.[17] Statistically significant superiority of NT 201 over placebo was also demonstrated when each domain (hygiene, dressing, pain, and limb position) was analyzed separately. Effects seem to be most

pronounced for the domain limb position and hygiene. The domain pain was the least commonly reported principle therapeutic target.

Previous placebo-controlled BoNT/A studies have provided mixed results about carer burden, where significant improvement was seen in 1 study,[19] trends,[23,24] or no improvement[21] in other trials. Significant reduction of some relevant tasks of carer burden was observed in this study for patients treated with NT 201.

Previous studies comparing NT 201 to an active BoNT/A comparator have demonstrated a similar safety profile for both agents.[10,11,26,27] In this placebo-controlled study, administration of NT 201 was safe and well tolerated in a high dose of up to 435 U. Adverse effects were mostly mild in intensity and comparable to the placebo group. None of the AEs of special interest was considered related to NT 201 treatment, and no death was reported for patients under NT 201 treatment.

The lack of complexing proteins in NT 201 is expected to be of therapeutic advantage, especially in patients requiring long-term treatment with high dosages such as patients with poststroke spasticity. Despite a high-maximum NT 201 dose of up to 435 U, none of the patients developed botulinum toxin neutralizing antibodies after treatment. Further studies investigating repeated treatments with NT 201 and development of neutralizing antibodies will be necessary to make definitive conclusions.

In conclusion, NT 201 led to statistically significant reductions in disability, muscle tone, and caregiver burden and was well tolerated in patients with poststroke upper limb spasticity.

ACKNOWLEDGMENTS

The authors like to thank Elke Grosselindemann (Brett Medical Writing, Australia) for the editorial assistance.

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