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Efficacy and Safety of Botulinum Type A Toxin (Dysport) in Cervical Dystonia: Results of the First US Randomized, Double-Blind, Placebo-Controlled Study

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Abstract: Botulinum toxin type A (Dysport) has been shown in European studies to be a safe and effective treatment for cervical dystonia. This multicenter, double-blind, randomized, controlled trial assessed the safety and efficacy of Dysport in cervical dystonia patients in the United States. Eighty patients were randomly assigned to receive one treatment with Dysport (500 units) or placebo. Participants were followed up for 4 to 20 weeks, until they needed further treatment. They were assessed at baseline and weeks 2, 4, 8, 12, 16, and 20 after treatment. Dysport was significantly more efficacious than placebo at weeks 4, 8, and 12 as assessed by the Toronto Western Spasmodic Torticollis Rating Scale (10-point vs. 3.8-point reduction in total score, respectively, at week 4; $P \leq 0.013$). Of participants in the Dysport group, 38% showed positive treatment response, compared to 16% in the placebo group (95% confidence interval, 0.02–0.41). The median duration of response to Dysport was 18.5 weeks. Side effects were generally similar in the two treatment groups; only blurred vision and weakness occurred significantly more often with Dysport. No participants in the Dysport group converted from negative to positive antibodies after treatment. These results confirm previous reports that Dysport (500 units) is safe, effective, and well-tolerated in patients with cervical dystonia. © 2005 Movement Disorder Society

Key words: cervical dystonia; spasmodic torticollis; botulinum toxin; Dysport; clinical trial

Focal dystonias are abnormal contractions of muscles leading to abnormal postures. The overactivity of muscles characteristic of focal dystonia is thought to be mediated by a neurophysiological disturbance in the basal ganglia and/or brainstem.[1,2] Cervical dystonia is the most common type of focal dystonia encountered in neurological practice, with a prevalence of eighty-nine affected patients per one million individuals.[3] It is characterized by sustained involuntary contractions of the cervical muscles, often leading to painful and disabling neck spasms and abnormal head positions. Rotation (tor-

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ticollis) and tilt (laterocollis) of the chin, forward flexion (anterocollis) or extension of the head (retrocollis) can be present either in isolation or in various combinations. At present, the treatment of choice for cervical dystonia is botulinum toxin injections.

There are two preparations of botulinum type A toxin (Dysport, Ipsen, Slough, UK, and BOTOX, Allergan, Irvine, CA) commercially available. The potency of both products is expressed in units, but the units for each product were derived in different assays. Controlled studies that have compared the efficacy and safety of these two products have demonstrated that 3 units of Dysport are roughly equivalent to 1 unit of BOTOX.[4,5]

Currently, only BOTOX is licensed for use in the United States, although Dysport has been commercially available outside the United States since 1990, and it currently is marketed in over 50 countries. Early randomized controlled trials demonstrated that Dysport was a safe and effective treatment for cervical dystonia,[6,7] and that it was superior to treatment with oral anticholinergic medications.[8] A dose ranging study of the efficacy and safety of 250, 500, and 1,000 units of Dysport in botulinum toxin-naive patients demonstrated that both efficacy and side effects were dose-related. Based on considerations of the balance between clinical benefit and side effects of the different doses, an optimal initiation dose of 500 units was recommended for this patient population.[9]

The purpose of this double-blind, randomized placebo-controlled trial was to replicate the safety and efficacy findings of the previous European study with respect to a fixed dose of Dysport. This large, multi-site trial is the first study of its kind to characterize the efficacy and immunoreactivity of Dysport for cervical dystonia in Dysport-naive patients in the United States.

PATIENTS AND METHODS

Participants

Male and female patients diagnosed with cervical dystonia were recruited from movement disorders clinics experienced in using botulinum toxin. Individuals who reported having had symptoms for at least 18 months were screened for eligibility. Patients were screened for health status with laboratory blood and urine tests, electrocardiogram (ECG), and a clinical history and physical examination. They also were evaluated using the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS).[10]

Patients were excluded from participating if they had clinically significant findings on hematology, serum biochemistry, urinalysis, or ECG tests; known significant underlying dysphagia that might be exacerbated by botulinum toxin treatment; diagnosis of myasthenia gravis, any disease of the neuromuscular junction (other than cervical dystonia), or a clinically significant, persistent neurological disorder; weighed less than 100 pounds (45.4 kg); or were pregnant or lactating. Individuals also were excluded if the study physician suspected secondary nonresponsiveness; if patients had had previous phenol injections to the neck muscles, myotomy, or denervation surgery involving the neck or shoulder region; or if they had cervical contracture that limited the passive range of motion. Finally, patients were not allowed to participate if they had a TWSTRS-Total score of less than 30, a severity score of less than 15, a disability score of less than 3, and a pain score of less than 1.

There were also exclusion criteria related to previous botulinum toxin exposure and to dose requirements. Patients who had been treated previously with botulinum toxin (either type A or B) were excluded from participating, unless it had been at least 16 weeks since their last injection. This study examined the effects of an initial fixed dose of Dysport (500 units).[11] To avoid recruiting participants for which this dose would likely be subtherapeutic or have the potential to cause excessive side effects based on previous dosing experience with BOTOX, the study excluded patients believed to require a BOTOX dose of <80 or >250 units. Exclusionary doses were derived from the proposed efficacy ratio of 3 to 1 between units of BOTOX and units of Dysport.[4,5] Patients with pure retrocollis were not permitted to participate, because they frequently require high doses. All patients provided written informed consent before participating in this study.

Study Design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel group, outpatient study. Sixteen centers, distributed throughout the United States, participated in the study. The number of patients per site varied from 2 to 21, depending on clinic capacity and recruitment success. After a 1-week screening period, eligible participants were randomly assigned to treatment with Dysport (500 units) or placebo. Post-treatment assessments were performed at weeks 2 (telephone contact only), 4, 8, 12, 16, and 20, or until additional injections were clinically indicated (study termination). For most patients, study termination occurred before week 16. The study physician evaluated participants for treatment efficacy and safety at each visit. The evaluation included physical and neurological examinations, vital signs, laboratory blood and urine tests, clinician ratings of efficacy, and adverse events. Participants completed a pain rating scale and a scale assessing changes from baseline

and kept a log of adverse events. Blood samples taken at baseline and end of study were tested for the presence of neutralizing antibodies. Participants who showed no benefit at week 4 were terminated from the study. Those who had evidence of response at week 4 continued in the study until additional injections were needed. Participants who completed the study (i.e., made it to week 4 or beyond) were invited to enroll in an open-label extension study, which will not be described here.

Study Medication

Dysport was provided in a clear glass vial as a freeze-dried white pellet containing a nominal (labeled) 500 units (range, 400–500 units) of *Clostridium botulinum* type A toxin–hemagglutinin complex together with 125 μg of human albumin and 2.5 mg of lactose. For purposes of comparison, BOTOX contains 0.9 mg of sodium chloride and 0.5 mg of albumin per 100 units. Placebo was provided in identical clear glass vials, containing 125 μg of human albumin and 2.5 mg of lactose. Study medication was supplied in individual patient boxes, containing one vial of either Dysport or placebo. Study medication was administered by intramuscular injection into two, three, or four clinically indicated neck muscles in a single dosing session, with or without electromyographic guidance. The investigator determined the number of injection sites per muscle and the dose at each site.

Concomitant Medication

Participants were not allowed to receive any botulinum injections other than those administered in the study. They also were not permitted to use any investigational new drug or device, aminoglycoside antibiotics, or any other drug that interferes with neuromuscular transmission or that might interfere with evaluation. Every effort was made to keep the dose of allowable concomitant cervical dystonia medication constant throughout the study. Muscle relaxants and benzodiazepines were permitted if the dose had been stable for 6 weeks before study entry and was expected to remain stable. A short course of such medication was allowed if required for patient care during the study.

Efficacy Assessments

TWSTRS Ratings.

The Toronto Western Spasmodic Torcollis Rating Scale (TWSTRS)-Severity (range, 0–35), -Disability (0–30), and -Pain (0–20) subscales assessed distinct aspects of cervical dystonia. The TWSTRS-Total score (0–85) reflected the sum of the three subscale scores. A decrease in TWSTRS-Total or subscale score indicates an improvement in the patient's cervical dystonia. To minimize the impact of interrater variability, the same investigator at each site assessed patients at each visit.

Pain Ratings.

Pain was evaluated with the Pain subscale of the TWSTRS and with a self-report visual analogue scale (VAS). At each visit, participants were asked to rate their pain (on average) during the week preceding treatment on a scale of 0 mm (least possible pain) to 100 mm (worst possible pain) by drawing a single vertical slash through the line at the point that best represented the severity of their pain.

Patient/Investigator Change Ratings.

At each post-treatment visit, patients and investigators independently assessed the change from baseline in the signs and symptoms of cervical dystonia on a visual analogue scale (0 mm to 100 mm). The middle of the scale indicated no change (50 mm), and the two extremes were symptom-free (100 mm) and much worse (0 mm).

Safety Assessments

Participants were asked to keep an adverse event log for the first 4 weeks after treatment, and they were contacted by telephone after 2 weeks to evaluate adverse events. At each assessment, participants were asked a nonleading question to elicit reports of adverse events. In addition, they were assessed according to a checklist of 10 conditions potentially associated with botulinum toxin therapy of neck muscles (dysphagia, dry mouth, voice alterations, neck muscle weakness, jaw weakness, myasthenia, tiredness, dyspnea, discomfort at injection site, visual difficulties). Whenever possible, an investigator or research nurse other than the one performing the TWSTRS assessment who was blind to treatment condition performed the assessment for adverse events. All sites were asked to achieve as much consistency as possible with respect to assessors. Physical and neurological examinations, assessment of vital signs, and standard laboratory analyses of hematology, serum biochemistry, and urinalysis also were conducted regularly. All adverse events were recorded regardless of their relationship to study medication. Plasma samples taken at baseline and on completion of the study were tested for the presence of neutralizing antibodies to Dysport using the mouse LD50 bioassay (Wickham Laboratories, Fareham, UK).

Statistical Methods

The study required a minimum of 60 patients (30 per treatment group) to be evaluable for the primary efficacy endpoint. With 30 patients in each group, there was a

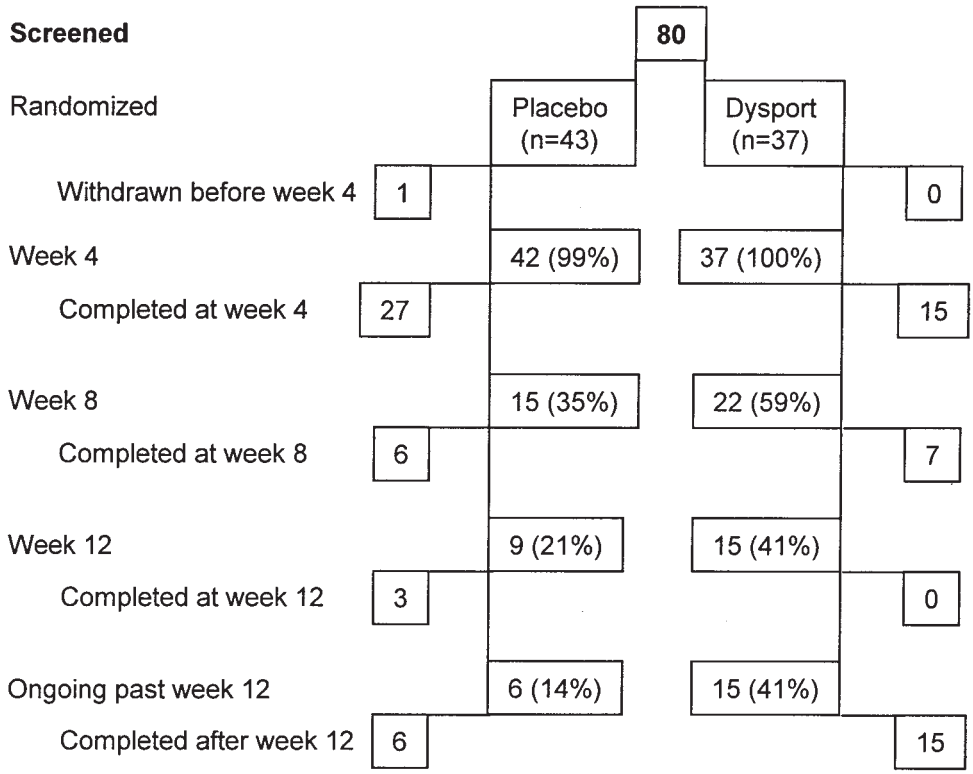

FIG. 1. Participant disposition.

greater than 90% chance of detecting a difference of 9 points on the TWSTRS Total scale with a two-sided -test ($P = 0.05$). This prediction assumes that the standard deviation (SD) of the difference in TWSTRS-Total score from baseline was 10 points, which was similar to the SD found by Lew and colleagues[12] All patients were randomly assigned to treatment using a randomization code generated before the study. Randomization was in blocks of four and was stratified by center and according to whether or not the patient had been treated previously with botulinum toxin. Centers were supplied with blocks of study medication as required.

The primary efficacy endpoint was the change in TWSTRS-Total score at week 4 compared with baseline. Secondary endpoints were the change in the pain VAS and patient assessment of signs and symptoms at week 4 compared with baseline. All other endpoints were considered tertiary. Prospective criteria defined a responder as a participant experiencing a decrease in TWSTRS-Total score of at least 30% and at least 10 points.

Statistical testing was performed for the primary and secondary endpoints, as well as the week 8 and week 12 time points for these variables. All statistical testing was two-sided and performed using a 5% significance level. Analysis of covariance (ANCOVA) was used for all efficacy analyses. Each analysis was adjusted for center, treatment history (previous botulinum toxin treatment or no previous botulinum toxin treatment), and baseline (where appropriate). All covariates remained in the final model, regardless of significance. Missing data at weeks 4, 8, and 12 were imputed using the patient's own baseline value for TWSTRS-Total and subscale analyses and for the pain VAS analyses. However, the patient/investigator assessment of change in signs and symptoms was not assessed at baseline; therefore, missing data were imputed with a value of 40 mm (on a 100-mm scale) to indicate moderate worsening. This conservative approach assumed that there was no dramatic improvement or worsening in withdrawn patients.

The primary safety analysis was the comparison of adverse event profiles between the Dysport and placebo groups, using a χ^2 or Fisher's exact test, with respect to the overall incidence of any adverse event that occurred with a frequency >5% in either treatment group. Center was included as a covariate in all analyses. Analyses were conducted with the *Statistical Analysis System* (SAS) *Release 6.12 TS065* under *Windows NT*.

RESULTS

Participant Disposition

Patient disposition is summarized in Figure 1. One participant in the placebo group withdrew from the study

TABLE 1. *Demographic and baseline characteristics*

	Placebo (n = 43)		Dysport (n = 37)	
	Mean (SD)	Median (range)	Mean (SD)	Median (range)
Age (yr)	53.6 (12.1)	53.0 (27–76)	53.4 (11.6)	56.0 (27–78)
Female, n (%)	27 (63)		23 (62)	
Caucasian, n (%)	40 (93)		30 (81)	
Weight (kg)	74.5 (17.7)	70.0 (46–112)	76.1 (13.9)	76.6 (52–110)
Height (cm)	169.2 (10.2)	169.0 (150–192)	167.5 (10.7)	168.0 (139–188)
Time since first diagnosis of cervical dystonia (mo)	68.3 (62.8)	64.0 (0–307)	84.6 (85.4)	69.0 (2–288)
Time since onset of signs/symptoms (mo)	140.3 (115.4)	120.0 (21–564)	145.7 (114.4)	114.0 (13–399)
De novo, n (%)	12 (28)		9 (24)	
Time since first botulinum toxin treatment (mo)	52.6 (30.7)	59.0 (9–108)	52.7 (38.9)	46.5 (3–156)
Botulinum toxin treatments (n)	12.3 (9.7)	9.0 (2–35)	9.3 (9.8)	6.0 (1–35)
Time since most recent botulinum toxin treatment (days)	217.8 (279.8)	143.0 (106–1582)	302.6 (349.0)	158.0 (111–1467)
Most recent dose of BOTOX (units)	210.9 (58.6)	200.0 (100–300)	232.1 (82.4)	252.5 (65–400)

before week 4. This participant completed the week 2 telephone safety assessment but refused to attend subsequent clinic visits. Substantially more placebo patients (27 of 43, 63%) than Dysport patients (15 of 37, 41%) ended their participation at week 4. Only 6 of 43 (14%) of the participants in the placebo group remained in the study after week 12, compared with 15 of 37 (41%) of those in the Dysport group ($P < 0.007$).

Demographic and Baseline Characteristics

Table 1 shows the demographic and treatment-related characteristics of participants in the placebo and Dysport groups. As is evident from the table, disease history and previous botulinum toxin exposure were similar for both treatment groups at baseline. The majority of participants in both groups were female, Caucasian, and had received prior treatment with botulinum toxin.

Efficacy

TWSTRS Scores.

TWSTRS data are presented in Table 2. As the table shows, there was a statistically significant improvement from baseline to week 4 on TWSTRS-Total score in the Dysport group but not in the placebo group. At week 4, the TWSTRS-Total score had improved for 29 of 37 (78%) of participants receiving Dysport compared to only 24 of 43 (56%) of participants receiving placebo. The mean change from baseline (i.e., baseline score minus week 4 score) on total scores at week 4 was 9.9 in the Dysport group, compared to 3.8 in the placebo group ($P \leq 0.013$). The improvement in the TWSTRS-Total score at week 4 was due to statistically significant decreases on all three subscales in the Dysport group. Although maximum improvement was observed at week 4, decreases in TWSTRS-Total scores for the Dysport group were still reduced by an average of 5.8 points at week 12 ($P \leq 0.02$ for differences within treatment group across time point).

Pain Ratings.

Table 2 also shows changes in VAS pain ratings as a function of treatment group and time. Pain ratings decreased by 13.4 mm at week 4 in the Dysport group but decreased by only 1.9 mm in the placebo group ($P \leq 0.02$). The marked reduction in pain ratings in the Dysport group was sustained through week 8.

Change Ratings.

Table 3 summarizes the patient- and investigator-rated assessments of change in signs and symptoms. At week 4, neither participants nor clinicians reported any apparent change in signs and symptoms in the placebo group. In contrast, both recorded marked improvement in the Dysport group. This group difference was statistically significant. Overall, at week 4, 14 of 37 (38%) of Dysport patients and 7 of 43 (16%) placebo patients reported an improvement of at least 50% over baseline (95% confidence interval [CI], 0.02–0.41). By week 12, ratings

TABLE 2. *TWSTRS and Pain Visual Analogue Scale*

	Placebo (n = 43)	Dysport (n = 37)	ANCOVA Analysis		
			Mean	CI	*P*
TWSTRS-Total					
Baseline	46.2 (9.4)	45.1 (8.7)			
Week 4	42.4 (12.2)	35.2 (13.8)	−6.0	−10.6, −1.3	0.013
Week 8	44.0 (11.6)	37.0 (13.8)	−5.8	−9.9, −1.6	0.007
Week 12	44.6 (11.5)	39.3 (12.9)	−4.3	−8.2, −0.4	0.030
TWSTRS-Severity					
Baseline	20.5 (3.4)	19.7 (2.6)			
Week 4	18.4 (4.8)	15.1 (5.8)	−2.5	−4.5, −0.5	
Week 8	18.8 (4.6)	15.9 (6.1)	−2.1	−4.0, −0.2	
Week 12	19.5 (4.5)	17.4 (5.2)	−1.3	−3.0, −0.4	
TWSTRS-Disability					
Baseline	14.1 (5.1)	13.9 (4.4)			
Week 4	13.5 (4.9)	11.4 (5.6)	−1.9	−3.5, −0.4	
Week 8	13.8 (5.4)	11.8 (5.5)	−1.9	−3.2, −0.5	
Week 12	13.9 (5.2)	12.2 (5.2)	−1.5	−2.8, −0.2	
TWSTRS-Pain					
Baseline	11.7 (3.8)	11.5 (3.8)			
Week 4	10.5 (4.8)	8.7 (5.5)	−1.6	−3.6, −0.3	
Week 8	11.4 (4.4)	9.4 (5.5)	−1.0	−3.6, −0.1	
Week 12	11.2 (4.4)	9.7 (4.9)	−1.4	−2.6, −0.2	
Pain VAS					
Baseline	52.9 (25.0)	48.6 (24.6)			
Week 4	51.0 (26.9)	35.2 (22.3)	−11.4	−21.3, −1.5	0.024
Week 8	53.9 (26.3)	41.2 (27.2)	−8.8	−16.4, −1.1	0.025
Week 12	52.0 (26.5)	45.5 (28.5)	−2.2	−8.3, 3.9	0.480

ANCOVA analyses are presented as the difference between the adjusted mean changes from baseline for Dysport and placebo with 95% confidence interval. Inferential statistics were not calculated for the TWSTRS subscale scores.

TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale; ANCOVA, analysis of covariance; VAS visual analogue scale; CI, confidence interval.

of the signs and symptoms had nearly returned to baseline in the Dysport group but remained significantly worse than baseline in the placebo group.

Duration of Response

More than twice as many Dysport patients (14 of 37, 38%) as placebo patients (7 of 43, 16%) met the criteria for a therapeutic response (difference in proportion of responders, 0.22; 95% CI, 0.02–0.41). The duration of the response was defined as the number of weeks between treatment and the recurrence of symptoms, as defined by a return of the TWSTRS-Total score to within 10% of baseline. For the patients who responded to Dysport, the mean (±SD) duration of the response was 22.8 (12.5) weeks and the median duration was 18.5 weeks. The large standard deviation reflects the variable treatment duration of several outliers (range, 9–46 weeks).

TABLE 3. *Assessment of change in cervical dystonia signs and symptoms*

	Placebo (n = 43)	Dysport (n = 37)	ANCOVA analysis		
			Mean	CI	*P*
Patient assessment					
Week 4	48.6 (20.4)	65.0 (19.2)	15.0	6.3, 23.7	<0.001
Week 8	46.4 (13.5)	59.8 (21.0)	12.9	4.9, 20.9	0.002
Week 12	43.6 (9.5)	51.9 (19.9)	8.4	1.2, 15.5	0.022
Investigator assessment					
Week 4	52.4 (14.9)	66.2 (20.3)	13.8	5.9, 21.6	
Week 8	47.7 (13.9)	58.0 (19.8)	10.4	2.8, 17.9	
Week 12	43.4 (10.0)	51.2 (19.5)	7.9	1.1, 14.6	

ANCOVA analyses are presented as the difference between the adjusted means for Dysport and placebo with 95% confidence interval. Inferential statistics were not calculated for the investigator assessment.

ANCOVA, analysis of covariance; CI, confidence interval.

TABLE 4. *Neutralizing antibody status*

	Placebo (n = 43)		Dysport (n = 37)	
	Baseline	Post-treatment	Baseline	Post-treatment
Negative	35 (90%)	32 (91%)	32 (89%)	31 (89%)
Positive	4 (10%)	3 (9%)	4 (11%)	4 (11%)
Not recorded	4	8	1	2

Data presented as the number (%) of patients. The denominator for the percentage calculation excludes patients without a test result.

Neutralizing Antibody Formation

Table 4 shows the number of participants in each group who were positive and negative for the presence of neutralizing antibodies. Overall, 8 of 75 (11%) participants were positive for neutralizing antibodies at baseline, with similar proportions in each group. All participants who tested positive previously had received BOTOX (8 of 59, 14%). For the 4 Dysport participants who tested positive at baseline, the mean (±SD) TWSTRS-Total score was 43.4 (±6.2) at baseline and 36.3 (±7.2) at week 4. This finding is in contrast to a reduction from 45.3 (±9.0) to 35.0 (±14.4) in patients who tested negative for blocking antibodies. Of the 4 patients with antibodies, 3 showed a similar response to the placebo group (mean change, 5.5 points). Only one patient with positive antibodies met criteria for a therapeutic response (reduction of 12 points, 32%). A total of 34 Dysport patients and 32 placebo patients had data both at baseline and also after treatment. No patients converted from negative to positive after treatment. One placebo patient converted from positive (low titer) to negative.

Adverse Events

Of participants treated with Dysport, 92% reported a total of 187 adverse events (5.5 events/patient), compared with 79% of patients receiving placebo, who reported 159 adverse events (4.7 events/patient). Adverse events with an incidence of >5% in the Dysport group are presented in Table 5. Adverse events with a ≥10% higher incidence in the Dysport group than in the placebo group were injection site pain (14.6%), blurred vision (13.5%), and muscle weakness (10.8%). Of these adverse events, both blurred vision and muscle weakness showed statistically significant differences between groups. Adverse event intensity was similar for Dysport (mild 49%, moderate 36%, severe 13%, disabling <1%) and placebo (mild 47%, moderate 37%, severe 16%). On completion of the study, only 1 patient decided not to receive Dysport treatment in the open label phase as a result of adverse events; this patient experienced severe dysphagia, moderate dry mouth, mild voice alteration, tiredness, and neck muscle weakness.

DISCUSSION

This randomized, controlled trial demonstrated that Dysport (500 units) is clinically and statistically more effective than placebo in a population of cervical dystonia patients. Dysport was well-tolerated and produced

TABLE 5. *Adverse events*

	Placebo (n = 43)	Dysport (n = 37)	Analysis		
			Mean	CI	*P*
Neck/shoulder pain	13 (30%)	14 (38%)	7.6	−13.2, 28.4	0.473
Injection site pain	10 (23%)	14 (38%)	14.6	−5.5, 34.7	0.156
Tiredness	13 (30%)	13 (35%)	4.9	−15.7, 25.5	0.641
Headache	10 (23%)	9 (24%)	1.1	−17.7, 19.8	0.911
Dry mouth	8 (19%)	8 (22%)	3.0	−14.6, 20.7	0.737
Neck muscle weakness	5 (12%)	6 (16%)	4.6	−10.7, 19.8	0.552
Dysphagia	4 (9%)	6 (16%)	6.9	−7.8, 21.6	0.501
Neck rigidity	4 (9%)	5 (14%)	4.2	−9.8, 18.2	0.726
Blurred vision	0	5 (14%)	13.5	2.5, 24.5	0.018
Voice alteration	4 (9%)	4 (11%)	1.5	−11.7, 14.8	1.000
Dyspnea	1 (2%)	4 (11%)	8.5	−2.5, 19.5	0.176
Insomnia	1 (2%)	4 (11%)	8.5	−2.5, 19.5	0.176
Muscle weakness	0	4 (11%)	10.8	0.8, 20.8	0.042
Viral infection	2 (5%)	4 (11%)	6.2	−5.7, 18.0	0.407
Dizziness	2 (5%)	3 (8%)	3.5	−7.4, 14.3	0.658
Back pain	3 (7%)	3 (8%)	1.1	−10.5, 12.8	1.000
Sinusitis	1 (2%)	3 (8%)	5.8	−4.1, 15.7	0.331
Bronchitis	1 (2%)	3 (8%)	5.8	−4.1, 15.7	0.331
Rhinitis	1 (2%)	3 (8%)	5.8	−4.1, 15.7	0.331

Analyses are presented as the difference between the percentage incidence for Dysport and placebo with 95% confidence intervals.
CI, confidence interval.

marked and relatively sustained reduction in pain, signs, and symptoms throughout the study.

An important aspect of this study was the use of a fixed dose of Dysport. A fixed dose was tested to demonstrate how patients who had never received Dysport would respond to a standard starting dose. It is noteworthy that this dosing procedure differs significantly from that used in clinical practice, where doses are individualized for each patient. In light of this difference, it is likely that many of the participants in this study did not receive the optimal dose in the appropriate muscle. A proportion of participants probably received a subtherapeutic dose, whereas others received a supratherapeutic dose. Nevertheless, the use of a fixed dose was necessary, because there were no data on which to base dose optimization in these naive patients. Assuming that the most recent dose of BOTOX (mean 226 units) was the patient's optimal dose, then using the 3:1 conversion factor[4,5] suggests that the mean optimal dose of Dysport for these patients would be approximately 678 units (35% higher than received).

Efficacy was assessed with several different measures, although TWSTRS was identified a priori as the primary measure. TWSTRS is a widely used instrument for assessing cervical dystonia, and it correlates well with the Tsui scale, another widely published assessment method.[13] An important observation with respect to efficacy was that the improvement in the TWSTRS-Total score was the result of improvements in each of the three subscale scores. This pattern indicates that Dysport exerted multiple therapeutic effects, improving not only head position, but also pain and extent of disability.

It is clear from this and other studies that Dysport is an effective treatment for cervical dystonia. What is less clear is how long the response to treatment lasts and, therefore, how frequently patients must receive injections. Although the design of this study does not lend itself to analysis of treatment duration effects, some useful information can be gleaned because participants only remained in the study until they required another injection. Among participants who showed therapeutic benefit from Dysport, median treatment duration was 18.5 weeks. This duration is consistent with the earlier reports in studies with Dysport. Studies with BOTOX[14] have reported a treatment duration of at least 12 weeks.

An ongoing issue of clinical concern over the use of botulinum toxins is the possible development of treatment-related neutralizing antibodies that could compromise the effectiveness of future injections. Clinically, the presence of neutralizing antibodies is only suspected when patients receive less benefit than usual from treatments or when patients who typically respond cease to obtain any benefit. When these secondary nonresponsive patients are tested for neutralizing antibodies, approximately half are found to be positive, suggesting that there is not a direct correlation between loss of response and the development of antibodies. This apparent discrepancy suggests that other factors may underlie the change in responsivity or that the antibody assay is not sensitive enough to detect low titers of neutralizing antibodies.[15] Indeed, a recent review, including data from 303 patients who had received at least six Dysport treatments for cervical dystonia, showed that 18 showed secondary nonresponsiveness but only 2% of those had neutralizing antibodies.[16] In the present study, 14% of participants who previously had received treatment with BOTOX and were presumed to maintain responsiveness tested positive for neutralizing antibodies to Dysport. The implication of this finding is that antibodies to BOTOX cross-react with Dysport. The presence of antibodies to BOTOX clearly dampened the therapeutic response to Dysport. In 3 of 4 patients with antibodies at baseline, response to Dysport was similar to the average response to placebo, i.e., mean change of 5.5 points TWSTRS-Total score). Only 1 patient (in the placebo group) converted from positive to negative after treatment, and none converted from negative to positive. Thus, very little can be concluded about the incidence of neutralizing antibody formation with Dysport. A better impression of the conversion rate will be provided once patients have completed the three Dysport treatments in the open label extension study.

The data obtained in this study confirm the safety and tolerability of Dysport observed in previous studies.[5,6–8,10] Few side effects occurred with greater frequency in the Dysport group than in the placebo group. The side effects that were observed, including muscle weakness, are consistent with the notion that the majority of Dysport-related adverse events result from the spread of toxin away from the site of injection, causing unwanted chemodenervation in adjacent structures. It is noteworthy, therefore, that there were five reports of blurred vision in the Dysport group but none in the placebo group. Reports of blurred vision suggest that, in a small number of cases, Dysport may spread to the muscles of the eye when injected into the cervical musculature. Blurred vision has been reported as a side effect in numerous studies of botulinum toxin in patients with blepharospasm and other ophthalmic disorders.[17–19] The rate of adverse events might be expected to be even lower in patients who have received optimized doses. This adverse event profile does not differ noticeably from data reported with BOTOX treatment in cervical dystonia.[16]

In conclusion, this double-blind study has demonstrated that Dysport (500 units) is clinically and statistically more effective than placebo in population of cervical dystonia patients typical of those seen in US dystonia clinics. Treatment with Dysport significantly reduced pain and disability and was generally well tolerated. Future US studies with Dysport should explore the effects of different fixed and optimized doses on safety and efficacy measures as well as antibody formation.

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