International Society for Pharmacoeconomics and Outcomes Research (ISPOR), Baltimore, MD, 21–25 May 2011

Health-Related Quality-of-Life Improvements With Dysport in Cervical Dystonia

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Introduction

- Cervical dystonia (CD) is one of the most common focal dystonias[1,2] with a prevalence of 8.9 cases per 100,000 people.
- 16% to 25% of cases of CD are undiagnosed, and fewer than 200,000 Americans are thought to be affected[3].
- CD is characterized by sustained involuntary contractions of cervical muscles that lead to painful disabling postures.
- The diagnosis of CD is based on clinical signs and symptoms; deviation in head/neck posture; involuntary neck movements resulting in turn, tilt, and/or shoulder elevation; and neck pain.[4,5]
- Patients with CD face a lifetime of chronic visible disability, and previous studies have demonstrated impaired health-related quality of life (HRQOL).[6,7]
- Studies have established Dysport® for Injection (also known in the United States [US] as abobotulinumtoxinA), a botulinum toxin (BoNT) type A product, as a safe and effective treatment for CD, which has resulted in a level A recommendation.[8]
- Outside of the US, Dysport has been approved for CD, blepharospasm, hemifacial spasm, adult upper limb spasticity, adult lower limb spasticity, and equinus foot spasticity in children with cerebral palsy.
- In the US, Dysport was approved in April 2009 for the treatment of adults with CD to reduce the severity of abnormal head position and neck pain in both toxin-naïve and previously treated patients.
  - This approval was based on two double-blind, placebo-controlled studies (Truong et. al, 2010[9], N = 116; Truong et. al, 2005[10], N = 80), with a primary efficacy endpoint of change from baseline to week 4 in the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) total score.

Objective

- To evaluate improvements in HRQOL in patients with CD enrolled in a double-blind, placebo-controlled study

References

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Methods

Design

- Truong, 2010 (N = 116), an international multicenter, double-blind, randomized, placebo-controlled trial, was conducted to evaluate the safety and efficacy of Dysport for the treatment of CD.
- Patients were randomized either to 500 U Dysport, divided among two to four affected muscles, with or without electromyogram guidance, or placebo.
- Patients had to have a diagnosis of CD with symptoms for at least 18 months.
- TWSTRS scores requirements:
  - Total: ≥ 30
  - Severity: ≥ 15
  - Disability: ≥ 3
- Key exclusion criteria included:
  - Treatment with botulinum toxin serotype A (BoNT-A) or BoNT within 16 weeks
  - Any disease of the neuromuscular junction
  - Previous phenol injection to neck muscles
  - Myotomy or denervation surgery in the neck/shoulder region
  - Cervical contracture
  - Suspected secondary nonresponsiveness or a history of poor response to BoNT-A
- Patients with pure anterocollis or retrocollis, symptom remission at screening, symptoms that could interfere with TWSTRS scoring, or BoNT-A neutralizing antibodies were also excluded.

Evaluation

- The primary efficacy variable was the change from baseline of the TWSTRS total score 0 (= best value)–85 (= worst value) at week 4. The change from baseline of the TWSTRS total score at weeks 8 and 12 also was analyzed.
- Pain was evaluated with the Pain subscale of the TWSTRS and a self-reported pain visual analog scale (VAS).
- HRQOL was assessed using the SF-36 Health Survey (SF-36). SF-36 scores range from 0 to 100 with higher scores indicating better health. Participants were assessed at baseline and weeks 2, 4, 8, 12, 16, and 20 after treatment.

Statistical Analyses

- The change from baseline of the TWSTRS total score was analyzed by analysis of covariance (ANCOVA) where baseline TWSTRS score, strata (i.e., whether the patient was previously treated by BoNT), and study center were covariates.
- The change from baseline at week 4 was summarized using descriptive statistics (mean and standard deviation [SD]). Treatment comparison was performed using an ANCOVA model with treatment and stratum as main effect and baseline value as covariate.
- Changes from baseline at week 8 were analyzed for each of the eight SF-36 domains using an ANCOVA model with baseline value as covariate. This analysis included subjects who had data at both baseline and week 8.

Results

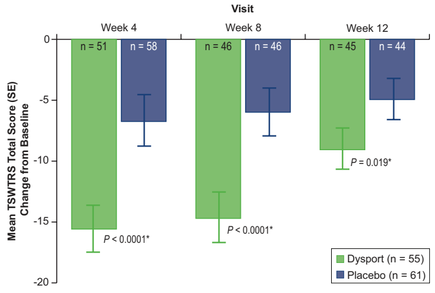
Table 1. Baseline Patient Characteristics

Characteristic	Dysport (n = 55)	Placebo (n = 61)
Age in years, mean (SD)	51.9 (13.4)	53.9 (12.5)
Female, n (%)	37 (67.0)	38 (62.0)
Caucasian, n (%)	55 (100)	61 (100)
Height, cm (SD)	167 (10.3)	170 (8.5)
Weight, kg (SD)	73.4 (13.8)	77.4 (15.0)
Non-naïve, n (%)	45 (82.0)	51 (84.0)

TWSTRS Total Score

- TWSTRS total mean scores were significantly improved with Dysport at weeks 4, 8, and 12 (P ≤ 0.019 compared with placebo) (Figure 1).

Figure 1. Mean (SE) Change in TWSTRS Total Mean Scores



SE = standard error.; *p < 0.05
Note: Change from baseline is expressed as adjusted least squares mean ± SE. Negative changes in score indicate improvement.

HRQOL

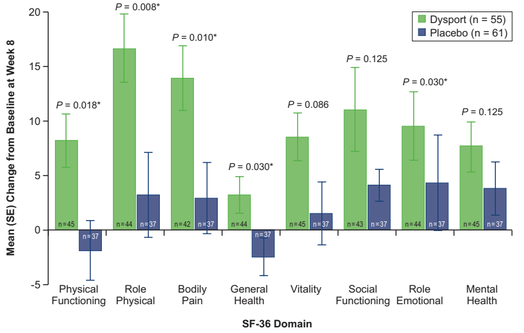
- Improvements from baseline to week 8 were observed for all eight SF-36 domains in the Dysport group (Table 2, Figure 1).
- The largest improvements occurred in the Role Physical and Bodily Pain domains.
- The placebo group showed some decline in Physical Functioning and little to no change in other SF 36 domains.
- The differences in mean change scores were statistically significant between Dysport and placebo for 5 of the 8 domains (Physical Functioning, Role Physical, Bodily Pain, General Health, and Role Emotional [P ≤ 0.03 for all]).

Table 2. Mean (SE) SF-36 Scores by Treatment Group: Baseline and Week 8

SF-36 Domain	Dysport N	Dysport Baseline Mean (SD)	Dysport Week 8 Mean (SD)	Dysport Change Mean (SD)	Placebo n	Placebo Baseline Mean (SD)	Placebo Week 8 Mean (SD)	Placebo Change Mean (SD)	P Value
Physical Functioning	45	61.9 (20.0)	70.1 (20.1)	8.2 (16.0)	37	68.2 (21.7)	66.4 (23.4)	–1.9 (16.8)	0.018
Role Physical	44	46.3 (28.5)	62.9 (25.1)	16.6 (21.1)	37	50.5 (29.9)	53.7 (25.6)	3.2 (24.0)	0.008
Bodily Pain	42	47.9 (23.0)	61.8 (20.4)	13.9 (19.7)	37	49.0 (19.7)	51.9 (22.0)	2.9 (20.3)	0.010
General Health	44	58.9 (19.4)	62.1 (18.4)	3.2 (11.1)	37	62.2 (19.6)	59.7 (21.1)	–2.5 (10.6)	0.030
Vitality	45	47.5 (15.6)	56.0 (16.8)	8.5 (15.0)	37	50.5 (19.5)	52.0 (19.2)	1.5 (17.8)	0.086
Social Functioning	43	62.2 (26.8)	73.3 (22.9)	11.0 (25.8)	37	63.2 (25.0)	67.2 (25.6)	4.1 (15.6)	0.125
Role Emotional	44	71.0 (25.4)	80.5 (21.5)	9.5 (20.9)	37	62.2 (28.0)	66.4 (25.3)	4.3 (26.8)	0.030
Mental Health	45	62.6 (16.3)	70.2 (15.8)	7.7 (14.5)	37	60.1 (20.9)	63.9 (21.0)	3.8 (15.2)	0.125

Note: Comparison between Dysport and placebo for change from baseline to week 8 using an ANCOVA model with baseline value as covariate.

Figure 2. Mean (SE) Change in SF-36 Scores at Week 8



SE = standard error; *p < 0.05; Note: Positive changes in score indicate improvement.

Pain

- Improvement in the SF-36 Bodily Pain domain also was supported by significant improvements in the TWSTRS Pain subscale (Table 3) and the pain VAS at week 4 (Table 4).

Table 3. Mean (SD) TWSTRS Pain Subscale Scores by Treatment Group

Visit	Mean (SD) Dysport (n = 55)		Mean (SD) Placebo (n = 61)		P Value
Baseline (week 0)	10.6 (3.8)	n = 55	10.9 (4.6)	n = 61	
Week 4	6.8 (5.1)	n = 53	9.3 (4.9)	n = 58	
Change from baseline	–3.7 (4.7)	n = 53	–1.3 (3.8)	n = 58	0.0017

Note: Values have been rounded to the nearest whole number. Negative changes in score indicate a reduction in pain.

Table 4. Mean (SD) Pain VAS Score by Treatment Group

Visit	Mean (SD) Dysport (n = 55)		Mean (SD) Placebo (n = 61)		P Value
Baseline (week 0)	47.4 (25.0)	n = 55	49.6 (24.5)	n = 57	
Week 4	29.3 (22.9)	n = 50	42.2 (26.4)	n = 57	
Change from baseline	–17.7 (24.4)	n = 50	–4.8 (24.6)	n = 53	0.0013

Note: Values have been rounded to the nearest whole number. Negative changes in score indicate a reduction in pain.

Conclusions

- **Treatment with Dysport resulted in significant improvements in the Physical Functioning, Role Physical, Bodily Pain, General Health, and Role Emotional SF-36 domains.**
- **Treatment with Dysport results in numerical improvements at week 8 for all eight SF-36 domains as compared with placebo.**
  - **While all domains showed directionally positive changes versus placebo, the lack of statistical significance in vitality, social functioning, and mental health MAY be due to fact that study was not powered to show differences on this tertiary endpoint**
- **As previously reported, Dysport also reduced pain in CD as measured by reductions in the TWSTRS Pain subscale and the pain VAS from baseline to week 4 compared with placebo.**
- **In this study, on the basis of a general quality of life measure and pain-specific scales, Dysport significantly improved HRQOL in patients with CD**

ACKNOWLEDGEMENT

This study was sponsored by Ipsen. We thank RTI Health Solutions for their medical writing services.