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Multicenter observational study of abobotulinumtoxinA neurotoxin in cervical dystonia: The ANCHOR-CD registry

Richard M. Trosch [a], Alberto J. Espay [b], Daniel Truong [c], Ramon Gil [d], Carlos Singer [e], Peter A. LeWitt [f], Mark F. Lew [g], Michele Tagliati [h], Charles H. Adler [i], Jack J. Chen [j], Dominic Marchese [k], Cynthia L. Comella [l,*]

[a] Oakland University William Beaumont School of Medicine, 32255 Northwestern Highway, Suite 40, Farmington Hills, MI 48334, United States
[b] Department of Neurology, UC Neuroscience Institute, University of Cincinnati, 260 Stetson Street, Cincinnati, OH 45267, United States
[c] The Parkinson's and Movement Disorder Institute, 9940 Talbert Avenue, Fountain Valley, CA 92708, United States
[d] Parkinson's Disease Treatment Center of Southwest Florida, 4235 King Highway, Port Charlotte, FL 33980, United States
[e] Center for Parkinson's Disease and Movement Disorders, Department of Neurology, University of Miami, Leonard M. Miller School of Medicine, 1150 NW 14th Street, Miami, FL 33136, United States
[f] Parkinson's Disease and Movement Disorders Program, Henry Ford Hospital, Wayne State University School of Medicine, 6777 W Maple Road, West Bloomfield, MI 48322, United States
[g] Division of Movement Disorders, Department of Neurology, University of Southern California, Keck School of Medicine, 1520 San Pablo Street #3000, Los Angeles, CA 90033, United States
[h] Department of Neurology, Cedars-Sinai Medical Center, 8631 W 3rd St #215e, Los Angeles, CA 90048, United States
[i] Department of Neurology, Mayo Clinic, 13400 E Shea Blvd, Scottsdale, AZ 85259, United States
[j] College of Pharmacy, Marshall B. Ketchum University, 2575 Yorba Linda Blvd, Fullerton, CA 92831, United States
[k] Ipsen Biopharmaceuticals, Inc., 106 Allen Rd, Basking Ridge, NJ 07920, United States
[l] Department of Neurological Sciences, Rush University Medical Center, 1725 West Harrison Street, Chicago, IL 60612, United States

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ABSTRACT

Background: The ANCHOR-CD prospective observational registry study evaluated the effectiveness of abobotulinumtoxinA in adult idiopathic cervical dystonia (CD) in clinical practice.
Methods: Adults with CD were eligible. Treating physicians determined abobotulinumtoxinA dose and treatment interval. The primary endpoint was patient response rate (Toronto Western Spasmodic Torticollis Rating Scale [TWSTRS] score reduction ≥ 25% and Patient Global Impression of Change [PGIC] score of +2 or +3 at Week 4 of Cycle 1).
Results: 350 patients enrolled (75% women; mean age 59 ± 13.6 years; 27.4% botulinum neurotoxin-naive) and 347 received at least 1 treatment. The median abobotulinumtoxinA dose for Cycle 1 was 500 Units. At Week 4, the responder rate was 30.6% (n = 304) and the TWSTRS total score decreased 27.4% from baseline. PGIC of at least "Much improved" was documented in 43.6% of patients and maintained in Cycles 2 through 4 (43.3%, 48.9%, and 52.8%, respectively). A total of 39 adverse events (31 study drug-related) were reported in 17 patients (5%); the most common were dysphagia (n = 6), muscle weakness (n = 4), and neck pain (n = 3).
Conclusion: This study confirmed the beneficial effect of abobotulinumtoxinA on CD in routine clinical practice as measured by improvements in TWSTRS and PGIC. No new safety concerns were identified.

1. Introduction

Cervical dystonia (CD) is a chronic movement disorder characterized by abnormal posturing or involuntary movements of the neck, head, and shoulders [1,2]. The movements observed in CD are often complex and can include rotation (rotocollis), flexion (anterocollis), extension (retrocollis), or tilting (laterocollis) [2,3]. In clinical practice, CD is heterogeneous in its presentation, with a wide range of symptom severity and patient comorbidities [3]. The disorder can have a major impact on patient quality of life [2,4].

CD is the most common adult-onset focal dystonia, with an estimated prevalence of 28–183 cases per million people in the general

Abbreviations: BoNT, botulinum neurotoxin; CD, cervical dystonia; CDIP, CD Impact Profile; CGIC, clinical global impression of change; PGIC, Patient Global Impression of Change; PNRS, Pain Numeric Rating Scale; TSQM, Treatment Satisfaction Questionnaire for Medication; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.

* Corresponding author.
E-mail addresses: richardtrosch@comcast.net (R.M. Trosch), espayaj@ucmail.uc.edu (A.J. Espay), dtruong@pmdi.org (D. Truong), drgil@parkinsonsfl.com (R. Gil), csinger@med.miami.edu (C. Singer), plewitt1@hfhs.org (P.A. LeWitt), mark.lew@med.usc.edu (M.F. Lew), michele.tagliati@cshs.org (M. Tagliati), cadler@mayo.edu (C.H. Adler), jchen@ketchum.edu (J.J. Chen), dominic.marchese@ipsen.com (D. Marchese), ccomella@rush.edu (C.L. Comella).

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population [3]. Geographical and ethnic differences may play a role in the wide range of prevalence estimates. For example, in a study of the multiethnic membership of a health maintenance organization in Northern California, prevalence of CD was higher in white patients of European descent than among Hispanic, Asian, or African-American patients [5].

Botulinum neurotoxin type A (BoNT-A) is established as an effective treatment for CD [6,7]. This neurotoxin inhibits the release of acetylcholine from the presynaptic neuron, inducing a graded muscle weakness. As a result of weakening dystonic muscles, there is a reduction in symptoms with improvement in pain and in control over voluntary head and neck movements. Relief is transient, and the effect wears off over the course of months [8,9].

AbobotulinumtoxinA (Dysport®, Ipsen Biopharmaceuticals, Inc., Basking Ridge, NJ, USA) is a BoNT-A indicated for the treatment of adults with CD [10]. The efficacy and safety of abobotulinumtoxinA for CD has been established in 2 randomized, controlled clinical trials and their open-label safety extensions [10–12]. Controlled studies, however, may not accurately reflect "real life" outcomes. Prospective naturalistic studies are needed to assess the effectiveness of treatment in routine daily practice, particularly in view of the heterogeneity of CD and the diversity in injection techniques by physicians across a variety of clinical practices.

ANCHOR-CD was a prospective, open-label, observational registry designed to evaluate the efficacy and safety of abobotulinumtoxinA for a 1-year period of repeated injections in adults with idiopathic CD treated in routine clinical practice in the United States.

2. Methods

2.1. Study population

Adult patients diagnosed with isolated (idiopathic) CD who gave their informed consent to participate were eligible for enrollment in the study. Patients could be BoNT-naïve or previously treated with BoNT if at least 12 weeks had elapsed since the last BoNT-A or BoNT-B injection. Patients were ineligible to participate if they had secondary CD, if they anticipated concomitant treatment with BoNT for indications other than CD, or if based on investigator opinion, previous BoNT-A or BoNT-B therapy had produced an insufficient response or intolerable adverse event (AE). The decision to prescribe abobotulinumtoxinA was to be made before and independently from the decision to enroll the patient in the registry. This study obtained appropriate institutional review board approval and was conducted under the provisions of the Declaration of Helsinki.

2.2. Treatment and assessments

AbobotulinumtoxinA was administered by intramuscular injection over 4 treatment cycles. The muscles selected for injection, the number of injections into each muscle, doses of BoNT, and method of administration were determined by the investigators in accordance with their standard of practice.

The recommended treatment cycle intervals in the study were consistent with the United States labeling for Dysport® (i.e., every 12 weeks). The treating physician determined the dose and treatment interval, taking into account patient response and label recommendations.

The primary efficacy endpoint was the patient response rate, defined as the percentage of patients with a Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) Severity scale score reduction of ≥25% in combination with a Patient Global Impression of Change (PGIC) score of +2 or +3 (much or very much improved) at Week 4 of Cycle 1.

Secondary endpoints included TWSTRS total and subscale scores, PGIC, Clinical Global Impression of Change scale (CGIC), time to waning effect of treatment, CD Impact Profile (CDIP-58), Pain Numeric Rating Scale (PNRS), and the modified Treatment Satisfaction Questionnaire for Medication (TSQM).

For the first injection (Cycle 1), in-office physician assessments were made at baseline and Week 4 following the injection. These assessments included the TWSTRS total and subscale scores (severity, disability, and pain). The TWSTRS Total score (maximum score of 85) was derived from the sum of the TWSTRS Severity score (0–35), the TWSTRS Disability score (0–30), and the TWSTRS Pain score (0–20). For the first cycle, CGIC was assessed at Week 4 using a 7-point Likert scale, ranging from +3 (very much improved) to −3 (very much worse). Because ANCHOR-CD was designed as a registry intended to capture data in a real-world, pragmatic setting, patients were not asked to come in to the office for physician assessments of efficacy after injection during Cycles 2 through 4. As a result, TWSTRS and CGIC data were only collected for Cycle 1.

Patient assessments of efficacy that were collected through all four cycles of treatment included PGIC, time to waning effect of treatment, PNRS, and the modified TSQM. PGIC was assessed using the same 7-point Likert scale for CGIC ranging from +3 ("very much improved") to −3 ("very much worse"). PGIC was assessed in the office at Week 4 of Cycle 1, during each subsequent treatment visit during Cycles 2 through 4, and at the study termination visit (no sooner than 12 weeks after the fourth treatment). PGIC was also assessed by phone interviews at Week 8 of Cycle 1 and Week 4 and Week 8 of Cycles 2 through 4.

Symptom reemergence was evaluated in-office at each treatment visit for Cycles 2 through 4 and at the study termination visit. It was assessed by phone interview at Week 8 of all four cycles.

The PNRS assessed pain during the previous 24 h on a scale of 0 (no pain) to 10 (worst possible pain). The PNRS was scored at each office visit and by phone interview 4 weeks after treatment for Cycles 2 through 4.

Satisfaction with treatment was assessed using the modified TSQM, an instrument with 6 questions assessing global satisfaction and effectiveness. Each question is rated on a 7-point scale ranging from "Extremely Satisfied" to "Extremely Dissatisfied". The modified TQSM was administered in-office at Week 4 of Cycle 1 and at the treatment visit for Cycles 2 through 4. It was also administered by phone at Week 4 of Cycles 2 through 4, and at the study termination visit.

The CDIP-58 is a validated 58-item patient-reported questionnaire assessing eight domains: head and neck symptoms, pain and discomfort, upper limb activities, walking, sleep, annoyance, mood, and psychosocial functioning. CDIP-58 was assessed at baseline, at the Cycle 3 treatment visit, and at the study termination visit.

Investigators were asked to report adverse drug reactions (ADRs, AEs thought to have a causative relationship to the drug) directly to the safety department of the study sponsor. AEs were reported to the study sponsor according to the regulations governing postmarketing reporting of spontaneous cases. In this paper, we include all ADRs and AEs reported to the sponsor from April 27, 2011 through April 22, 2014.

2.3. Statistical reporting

This was an observational study and thus did not include statistical significance testing. The response rate was calculated as the number of responders divided by the number of patients who completed TWSTRS and PGIC assessments at Week 4 of Cycle 1. An exact 95% confidence interval (CI) was calculated using the binomial distribution without a continuity correction. The 95% CIs of mean change were calculated using the normal approximation to the distribution of the sample mean. Demographic and efficacy data collected as continuous measures were summarized by mean, SD, median, 25th percentile, 75th percentile, minimum, and maximum.