Comparison of Methodology, Patient Characteristics, and Treatment Results from ANCHOR-CD (AbobotulinumtoxinA Neurotoxin: Clinical and Health Economics Outcomes Registry in Cervical Dystonia) and Other Registry Studies of Botulinum Toxin Type A in Cervical Dystonia

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Background

- Several randomized controlled studies have established the efficacy and safety of botulinum neurotoxin type-A (BoNT-A) products in the management of cervical dystonia (CD).[1, 2] However, while controlled studies are required for establishing the overall clinical efficacy of an intervention, they often leave several important clinical information gaps and do not provide accurate assessments of "real life" patient-related outcomes.[3]
- Prospective naturalistic studies are needed to fully assess the effectiveness of treatment in routine daily practice, particularly in view of the heterogeneity of CD clinical presentation and the diversity in the injection technique by physicians in clinical practice.
- In the US, there are currently three BoNT-A products approved for use in CD: abobotulinumtoxinA [aboBoNT-A; Dysport®, Ipsen, Paris, France], onabotulinumtoxinA [Botox®, Allergan, Irvine, CA, USA] and incobotulinumtoxinA [Xeomin®, Merz Pharmaceuticals GmbH, Frankfurt, Germany]. The formulation for each is proprietary, potentially affecting the pharmacological and biochemical characteristics of each product.[4] In addition, the units of activity are specific to each product and not interchangeable.
- Each of the three manufacturers of BoNT-A products have conducted "real world" open-label registry studies in the US to further establish the real world effectiveness of the product as well as investigating other clinical questions of interest.
  1. ANCHOR-CD was a prospective, open-label, US registry designed to collect patient response and health economics data in patients with CD who were treated with aboBoNT-A.[5,6]
  2. CD PROBE was a prospective, observational, multicenter, US registry designed to assess the safety, effectiveness, and treatment utilization following multiple treatments of onabotulinumtoxinA.[7]
  3. XCiDaBLE was a prospective, observational, naturalistic US study evaluating incobotulinumtoxinA for CD® or blepharospasm.[9]
- Decision makers are increasingly encouraged to include the results of registry studies and patient reported outcomes when performing comparative effectiveness reviews (CERs).[3, 10] Therefore, it is important to assess similarities and differences between registries.

Objective

- We aimed to assess similarities and differences between methodology, patient characteristics, and treatment results from registry studies of different BoNT-A formulations in the routine management of CD.

Methods

- Data from ANCHOR-CD (n=347) was compared with the published results of two other open-label registries, CD-PROBE (n=1041) and XCiDaBLE. Evaluations of the XCiDaBLE study focused on CD patients only (n=145[9]), as data from patients with blepharospasm was outside the scope of this assessment.
- Study methodology, patient, and treatment-level data were extracted and compared under predefined headings (Tables 1-4).

Results

Table 1. Methodologies

Similarities	Differences
All 3 studies included subjects with CD who the physician chose to treat with the relevant BoNT-A formulation prior to and independent of study enrollment.	CD-Probe inclusion criteria encouraged recruitment of BoNT naïve patients
The selection of BoNT-A dosage, dilution, muscles to be injected, and the use of guidance techniques were at the discretion of the treating physician.	**Number of treatment cycles:** • ANCHOR-CD: up to 4 injection cycles • XCiDaBLE: 2 injection cycles • CD-PROBE: up to 3 injection cycles
All 3 studies assessed: • Clinician Global Impression of Change (CGI-C) • Patient Global Impression of Change (PGI-C) • CD impact profile (CDIP-58) • Health economic data (varied outcomes)	The treatment interval was at the discretion of investigators in all 3 studies. **However:** • ANCHOR-CD specified that intervals should not be <12 weeks (in accordance with US prescribing recommendations) • XCiDaBLE allowed shorter treatment intervals of 6 weeks between the 1st and 2nd injections • CD-PROBE had no restrictions on dosing intervals
	• Unlike ANCHOR-CD and CD-PROBE, the XCiDaBLE study did not report the use of 1. Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) 2. Pain Numeric Rating Scale (PNRS)
	• XCiDaBLE is an interim analysis and did not include the whole data set, only the baseline and week 4 completed by the patient at home.

Table 2. Findings

Similarities	Differences
Mean (±SD) age (years): • ANCHOR-CD: 59.0 ± 13.6 • XCiDaBLE: 54.9 ± 12.6 • CD-PROBE: 58.0 ± 14.7	**Previous treatment with BoNT:** More patients in ANCHOR-CD and XCiDaBLE had previously received BoNT treatment vs. CD-PROBE • ANCHOR-CD: 73% • XCiDaBLE: 77% • CD-PROBE: 36.5%
Proportion of females: • ANCHOR-CD: 75% • XCiDaBLE: 82.3% • CD-PROBE: 74.4%	Changes in CDIP-58 subscale scores were similar between ANCHOR-CD and XCiDaBLE, but larger in CD-PROBE, possibly due to a higher proportion of BoNT-naive patients
Mean (±SD) age at onset (years): • ANCHOR-CD: 48.9 ± 15.6 • XCiDaBLE: 43.3 ± 13.7 • CD-PROBE: 49.0 ± 16.7	
Changes in TWSTRS scores (ANCHOR-CD vs. CD-PROBE)*: TWSTRS Total: -12.1 vs. -12.1 TWSTRS severity: -6.1 vs. -5.6 TWSTRS disability: -3.3 vs. -3.1 TWSTRS pain: vs. -2.6 vs. -3.4	
Proportion of patients much/very much improved on CGI-C • ANCHOR-CD: 62.7% • CD-PROBE: 61.4%** • XCiDaBLE: not reported	
Proportion of patients much/very much improved on PGI-C • ANCHOR-CD: 43.6% • CD-PROBE: 53%** • XCiDaBLE: 33.1%	

*ANCHOR-CD data: represent change from baseline to week 4 of cycle 1 (n=304), CD-PROBE data represent change from baseline to visit 3 (after 2nd injection) in patients who completed all TWSTRS assessments (n=476). **CD-PROBE data represent change from baseline to visit 2 (after 1st injection) in patients who completed all CGI-I (n=479) / PGI-I assessments (n=470).

Table 3. Dosing information from the studies (units of activity are specific to each product and not interchangeable)

	ANCHOR-CD	CD-PROBE	XCiDaBLE
Mean dose			
Cycle 1	503.6 ± 228.6U	171.6U	225.2 ± 150.8U
Cycle 2	545.8 ± 260.6U	199.6U	
Cycle 3	542.6 ± 263.6U	207.2U	
Cycle 4	551.7 ± 266.9U		
Mean # muscles injected			
Cycle 1	4.4 ± 1.3	8.7	Not reported
Cycle 2	4.5 ± 1.3	10.0	
Cycle 3	4.6 ± 1.4		
Cycle 4	4.6 ± 1.3		

Table 4. Adverse events of special interest

	ANCHOR-CD*	CD-PROBE	XCiDaBLE
Dysphagia	6 patients (1.8%)	65 patients (6.2%)	0
Muscular weakness	4 patients (1.2%)	65 patients (6.2%)	0
Neck Pain	3 patients (0.9%)	24 patients (2.3%)	reported but frequency is unclear**

*ANCHOR-CD did not collect AEs systematically. AEs were not collected at the beginning of the study, instead relying on investigators to report to the FDA. Hence, the frequency reported here is falsely low.
**In the XCiDaBLE study, 7 of 145 subjects reported an AE including: decreased joint range of motion, musculoskeletal pain, neck pain, and localized swelling (frequency counts not reported).[9]

Discussion/Conclusions

- Patient characteristics and response patterns were generally similar across the 3 BoNT-A US registries, supporting each BoNT-A effectiveness in the treatment of CD.
- Of note, it has been recently reported that BoNT naïve subjects tend to have higher TWSTRS and CDIP-58 total and subscores (Indicating greater impact) at baseline when compared to patients who have previously been treated.[11] CD-Probe enrolled a higher percentage of BoNT naïve patients and this may also be of relevance to the higher reported numbers of dysphagia and neck pain. Subgroup studies may be of interest.
- Given methodological, patient population, and endpoint differences between studies, no definitive comparative safety and efficacy conclusions can be drawn since methodologies, baseline patient characteristics, endpoints vary.
- The results of the ANCHOR-CD study have been included into the larger MetaCD database, which extends the database for aboBoNT-A to 1624 patients with primary CD treated across 35 countries.

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