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ORIGINAL ARTICLE

Pilot Single-Blind Trial of AbobotulinumtoxinA in Oromandibular Dystonia

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Abstract

Oromandibular dystonia (OMD) causes involuntary movements of masticatory and lingual muscles impairing eating, speaking, and swallowing. Treatment options are limited. The objective of this study was to determine the safety and efficacy of abobotulinumtoxinA (aboBoNTA) in OMD. A dose-finding study (phase 1) followed by a single session, prospective, single-blind trial (phase 2) was carried out. OMD subjects were evaluated at baseline, 6 and 12 weeks. Muscles injected were tailored to individual symptoms using EMG guidance, but the aboBoNTA dose for each muscle was pre-specified based on phase 1 results. Evaluations were Global Dystonia Rating Scale (GDS), Unified Dystonia Rating Scale (UDRS), Clinical Global Impression (CGI) improvement and severity, and quality of life (OMDQ-25). Adverse events were monitored. The lowest dosage in phase 1 resulted in adverse effects in two of three patients and thus was used in phase 2. In phase 2, adverse effects were observed in 50% of subjects including dysphagia, voice change, and soft palate weakness. Most were mild. Significant improvement was seen in quality of life (OMDQ-25), speech (BFMq21), and change in GDS, UDRS, CGI severity assessed by the unblinded investigator, but not in blinded video ratings. We conclude that aboBoNTA therapy in this study was associated with improved quality of life and was generally well tolerated in OMD, but occurrence of dysphagia dictated the importance of using low genioglossus dosing. Face to face assessment appears to be more sensitive than video assessment for change in OMD severity. Consideration of the disability in OMD places constraints on traditional placebo-control trial design. Development of novel trial designs is warranted.

Keywords Dystonia · Oromandibular dystonia · AbobotulinumtoxinA · Quality of life · Clinical trial

Introduction

Oromandibular dystonia (OMD) is a disabling form of dystonia involving the lower facial, masticatory, and lingual muscles. The diagnosis is often missed and treatment delayed for many years [1]. OMD results in involuntary movements including forced jaw opening, jaw closing, jaw deviation, jaw tremor, tongue protrusion, and facial grimacing each occurring either in mixed combinations or less commonly as separate entities [2–4]. In some patients, the movements are present only with action or tasks such as speaking or chewing [2], but OMD can also be present at rest [1].

The prevalence of isolated OMD has been estimated to be 0.8 to 6.9 per 100,000 [5, 6]. Prevalence estimates are higher when OMD is included as part of a segmental pattern of dystonia, such as "Meige's Syndrome." OMD can occur in combination with blepharospasm, spasmodic dysphonia, and cervical dystonia [2, 7]. Isolated OMD makes up 2 to 23% of cranial dystonias [7] and comprises 1 to 3% of all focal dystonias [8]. Age of onset is usually in the 6th or 7th decade, and women are affected more often than men [1, 9].

OMD patients are disabled by the interference of these movements with their ability to eat, speak, and swallow, and it causes

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pain, self-injury, and weight loss [10, 11]. Patients suffer from poor quality of life and increased social anxiety [12–14].

OMD responds poorly to oral medications, and oral appliances have limited impact [1, 15, 16]. Although botulinum toxin injections are considered the treatment of choice for most forms of focal dystonia, the literature in OMD is limited and consists of mostly open series and case reports along with two small-blinded studies [1, 17–19]. Approximately two thirds of patients are reported to respond to toxin therapy, which is substantially less than other focal dystonias [16]. There is a debate regarding injection patterns, toxin types, dosages, and efficacy for OMD with one report suggesting that treatment remains an unmet therapeutic need [1].

The objective of this study was to determine appropriate dosage range and to report on the safety and efficacy of abobotulinumtoxinA (aboBoNTA) for OMD in a prospective single-blind trial.

Methods

This pilot study was planned as a prospective, single-blind trial of aboBoNTA for the treatment of OMD (clintrials.gov NCT01921270). It was comprised of two phases: phase 1 for dose finding, phase 2 for safety and efficacy assessment of a single-dose session based on phase 1. The aims included the following: 1) determining the safe dose range of aboBoNTA for specific muscles in the treatment of OMD; 2) exploring the safety and efficacy of that dose administered in a single-dosage session among a larger cohort of subjects.

Study Population

The Emory University Institutional Review Board approved this study. Patients were consented at the time of enrolment. Patients were included if they were 18 years of age or older, had a diagnosis of idiopathic or tardive OMD as they respond similarly to toxin injections [20], had moderately severe OMD requiring toxin therapy (Global Dystonia Severity Rating Scale score for the jaw and tongue ≥ 4), had a history of therapeutic response to previous injection with any form of botulinum toxin type A (based on medical record review—all patients had been injected at Emory so those records were available), were at least 12 weeks past their last toxin injection, and used appropriate contraception if a woman of childbearing age. Dystonia was diagnosed according to currently accepted criteria [21] and involved abnormal movements or postures of the jaw, tongue, and lower face. Patients were excluded if they had a systemic disorder that could confound the evaluation, including concomitant neuromuscular disorder (e.g., myasthenia gravis, Lambert-Eaton syndrome, motor neuron disease); had concomitant treatment that could confound evaluation of efficacy, including deep brain stimulation; were receiving unstable dosages of medications to treat dystonia (e.g., benzodiazepines, baclofen, or anticholinergics); were receiving oral medications that could interfere with action of botulinum toxin (e.g., aminoglycosides); had a local infection at proposed injection sites; a history of immunoresistance to other forms of botulinum toxin type A; a history of hypersensitivity reaction to aboBoNTA and/or allergy to cow's milk protein; and women were excluded who were pregnant, breastfeeding, or of childbearing age unwilling to take oral contraception.

Study Design

Phase 1 was intended to be a 3×3 assessment [22] whereby 9 OMD subjects received 3 different dose levels of aboBoNTA (low, medium, and high; 3 in each group) using a step-wise approach based on safety response. This was followed by phase 2, which was to examine safety and efficacy of the dosage of aboBoNTA born out of phase 1 in a larger cohort of patients.

Injection Method

A percutaneous approach [11] using EMG guidance was used to inject each muscle. The muscles to be injected were tailored to individual OMD symptoms at the discretion and based on the experience of the injector. Muscles chosen to be included in the study are listed in Table 1. Each muscle chosen, however, was injected with a fixed dose of aboBoNTA diluted to 100 units/mL. Only OMD and lingual muscles were injected with the study toxin. As there was little literature on aboBoNTA use in OMD, the dose levels were developed based on the literature, particularly that from treating OMD

Table 1 Doses of AboBoNTA per muscle if selected for injection

	Low dose	Medium dose	High dose
Medial pterygoid	50	75	100
Masseter	25	50	75
Lateral pterygoid	50	75	100
Anterior digastrics	10	20	30
Genioglossus	15 (amended to 7.5)	25	35

in X-linked dystonia parkinsonism in the Philippines [11]. Dose ranges for each muscle were developed and then the range was subdivided into tertiles, low, medium, and high (Table 1). Each dose level was to be tested in phase 1.

Safety Assessments

Safety assessments for phase 1 and 2 were completed with standard open adverse event collection and a questionnaire regarding ease of chewing and swallowing (Swallowing Disturbance Questionnaire [SDQ]; max score 42) [23]. Severity of AEs was assessed by the reporting patient as mild, moderate, or severe based on functional impact. For example, mild swallowing problem would be noticed slowing of the swallow but no functional impact, moderate would mean dysphagia for a particular texture that limited their ability to eat that particular item but otherwise could eat and drink with minimal problem, and severe meaning many types of liquid and solids involved requiring pureed foot or thickened liquids.

Efficacy Assessment

Subjects were evaluated by blinded video assessment using a standardized video protocol (see supplementary material) as well as face to face assessments by the injecting physician. Video assessments were completed prior to injection (at baseline), 6 weeks following injection (peak effect) and 12 weeks following injection (trough effect). The severity of dystonia in these videos was scored in randomized order (devised by the statistician) by 3 blinded video raters who were movement disorder experts. Their scores were averaged for statistical analysis. Outcome measures included those scored by the blinded raters: the change in jaw/tongue portion of the Global Dystonia Severity Rating Scale (GDS; max score 10 [24]) and the Unified Dystonia Rating Scale jaw/tongue (UDRS; max score 8) [24] from baseline to week 6 and week 12; GDS and UDRS score changes at week 6 and 12 by the injecting investigator determined in a face to face assessment; and patient-related scores drooling (SCS-PD; max score 21) [25]; ease of speaking (Fahn-Marsden Scale Part B "Speech" question; DRS-21; max score 4 [26]); quality of life (QoL) (OMDQ-25; max score 100) [12]; clinical global impression (CGI) severity (max score 7); CGI improvement 1 = very much improved, 4 = no change, 7 = very much worse; CGI efficacy (takes into account efficacy ad adverse effects; 0–4 with 4 being the best response).

Statistical Analysis

This was a pilot study, so no power analysis was completed. We compared pre- versus post-intervention outcomes using 2-sided paired *t* tests. In this pilot study, no adjustment was made for multiple comparisons.

Results

Phase 1

Three subjects were enrolled in phase 1 for the initial lowest dose. Two subjects experienced adverse effects that were likely toxin related (subject 2 had throat tightness and speech change; subject 3 difficulty chewing, dysphagia, and soft palate weakness). Despite the mild nature of these AEs, it was determined that it was not safe to move to higher dosages. Low-level doses were used in phase 2 (Table 1).

Phase 2

Eighteen OMD patients were enrolled in phase 2, 15 idiopathic and 3 tardive. Eighteen subjects were assessed at week 6 and 17 subjects were assessed at week 12 (subject 12 withdrew after week 6 due to lack of efficacy). Demographic features are listed in Table 2. Mean age was 62.83 ± 10.45 years, and 67% were female. Mean duration of OMD was 73.89 ± 53.16 months. Nine patients had jaw-opening dystonia only, 3 had jaw-closing dystonia only, and 6 had a combination of jaw-opening and jaw-closing dystonia. Six had concomitant lingual protrusion dystonia.

Efficacy

Patient-reported quality of life as measured by the OMDQ-25 was significantly improved at week 12 ($p = 0.04$). The unblinded GDS and UDRS changes at weeks 6 and 12 were significantly improved compared to baseline ($p < 0.001$). The CGI severity score improved from moderate to mild symptoms at week 6 ($p = 0.002$) and week 12 ($p = 0.004$). CGI improvement was between minimal and much improvement at weeks 6 and 12 and CGI

Table 2 Patient demographics

Age	62.83 ± 10.45
% female	67
Duration of OMD (months)	73.89 ± 53.16
Diagnosis	15 idiopathic, 3 tardive
Type of OMD	6 jaw opening 3 jaw opening + lingual 2 jaw closing 1 jaw closing and lingual 4 jaw opening and closing 2 jaw opening and closing and lingual

Individual patient details are shown in supplementary Table X

efficacy which accounts for both improvement and adverse effects indicated overall a minimal improvement. All ratings by blinded video raters including the GDS change at weeks 6 and 12 compared to baseline, and UDRS change at weeks 6 and 12 compared to baseline, did not show significant changes following treatment (Table 3).

Safety

Adverse events were reported in 9 of 18 (50%) patients injected with aboBoNTA (Table 4). Of these, dysphagia was the most common affecting 6 patients, mild in 1 and moderate in 5. A safety evaluation after the first 10 subjects demonstrated that 4 of the first 5 injected for lingual dystonia developed dysphagia. At that point, the genioglossus dose was decreased from 15 units each to 7.5 units each. The others injected for lingual dystonia after the dosage change did not develop dysphagia. The SDQ did not show a significant change. Other adverse events were speech change (5 subjects), soft palate weakness (4 subjects), dry mouth (3 subjects), throat tightness (3 subjects), and drooling (3 subjects) (Table 4). Dosing injection patterns and associated adverse events for each case are detailed in supplementary materials (Supplementary Table).

Table 4 Adverse events reported in 9 of 18 patients

Adverse event	Mild	Moderate	Severe
Dysphagia	1	5	0
Speech change	3	2	0
Soft palate weakness	3	1	0
Dry mouth	2	1	1
Throat congestion/tightness	2	1	0
Drooling	3	0	0
Difficulty chewing	2	0	0
Food falling out of mouth	2	0	0
Coughing	1	1	0
Weight Loss	1	1	0
Flu-like symptoms	1	1	0

Severity of adverse event was subjectively rated by the investigator on face to face evaluation. There were no "Serious" adverse events, as defined by the FDA clinical trials guidelines

Discussion

In this prospective, single-blind trial, we examined 18 patients with OMD treated with aboBoNTA at a dose delineated by a prior dose finding study. Although this study was negative in relation to the blinded video efficacy assessment, we found several patient-related and unblinded outcome measures

Table 3 Outcome measures of severity following treatment

Outcome	Baseline (Mean ± SD)	Week 6 (Mean ± SD)	Week 12 (Mean ± SD)	Change from baseline	
				Week 6	Week 12
Patient measures					
Quality of Life (OMDQ-25)	47.39 ± 23.00	43.22 ± 23.24	38.00 ± 21.42	− 4.17 ($p = 0.19$)	− 9.39 ($p = 0.04$)
Speech (BFM-q21)	1.33 ± 0.91	0.94 ± 0.87	0.94 ± 0.75	− 0.39 ($p = 0.049$)	− 0.39 ($p = 0.03$)
Drooling (SCS-PD)	3.00 ± 3.91	2.72 ± 4.28	2.53 ± 3.20	− 0.28 ($p = 0.75$)	− 0.47 ($p = 0.55$)
Ease of chewing and swallowing (SDQ-20)	13.17 ± 9.54	15.61 ± 8.56	13.29 ± 8.54	2.44 ($p = 0.18$)	0.12 ($p = 0.72$)
Unblinded investigator face to face measures					
Unblinded UDRS jaw/tongue	4.67 ± 1.15	3.47 ± 1.58	3.26 ± 1.47	− 1.2 ($p < 0.001$)	− 1.41 ($p < 0.001$)
Unblinded GDS jaw/tongue	5.67 ± 1.53	3.94 ± 2.10	3.76 ± 2.25	− 1.73 ($p < 0.001$)	− 1.91 ($p = 0.001$)
CGI-severity	4.06 ± 1.00	3.22 ± 1.11	3.29 ± 0.92	− 0.84 ($p = 0.002$)	− 0.77 ($p = 0.004$)
CGI-improvement	n/a	2.89 ± 1.28	2.53 ± 0.87	n/a	n/a
CGI-efficacy	n/a	1.51 ± 0.93	1.93 ± 0.97	n/a	n/a
Blinded rater video assessment measures					
GDS jaw/tongue	3.80 ± 2.29	3.57 ± 2.05	3.71 ± 2.18	− 0.23 ($p = 0.61$)	− 0.09 ($p = 0.84$)
UDRS jaw/tongue	3.50 ± 1.92	3.47 ± 1.79	3.30 ± 1.72	− 0.03 ($p = 0.92$)	− 0.30 ($p = 0.58$)

demonstrated significant improvement. Most notably, QoL was significantly improved at the 12-week time point. Speech, as measured by the BFM question 21, was also significantly improved at both the 6- and 12-week time points. Unblinded GDS and UDRS scores assessed in person were also significantly improved. These findings support the potential utility of aboBoNTA for the treatment of OMD.

Though there have been few prospective controlled trials of any kind for OMD, 1 double-blind class II trial from 1987 using onabotulinumtoxinA for craniocervical dystonia demonstrated 37.5% improvement in a direct evaluation, 20% improvement in a video evaluation, and 7% improvement by self-assessment [18, 27]. One other class II placebo controlled, double-blind trial with aboBoNTA included 12 patients (6 active, 6 placebo) with nocturnal bruxism [28], which is not a typical form of OMD and not as troublesome. Most of the published data are retrospective. One study of 20 patients treated with onabotulinumtoxinA reported a 47% improvement in 19 of 20 patients [29]. Two other retrospective evaluations of lingual dystonia showed good responses. In one of them, up to 89% of sessions using onabotulinumtoxinA demonstrated improvement with adverse effects being uncommon although dysphagia was considered a concern [4, 30]. In the other, aboBoNTA was used in most of the 30 cases followed in a prospective observational trial and demonstrated an improvement in QoL [26]. Adverse events were dysphagia and respiratory issues. Perhaps the largest experience is in X-linked dystonia parkinsonism where 50 patients with OMD and 35 with lingual dystonia were treated with aboBoNTA. These patients demonstrated a substantial improvement in dystonia and pain [11]. Finally, a retrospective chart review for long-term responsiveness of OMD with onabotulinumtoxinA has demonstrated minimal morbidity and is useful for all forms of OMD [19]. Some data suggest that jaw-closing dystonia responds better to toxin therapy than jaw-opening dystonia [3, 31], but this remains to be confirmed prospectively.

One limitation in the treatment of OMD and design of prior trials is that dosing patterns are not well established. Another limitation is that there is no gold standard efficacy assessment of OMD. Our study provides guidance for future practice and research on muscle injection patterns, appropriate doses, and typical side effects. We found that change in GDS on blinded video assessments did not reach statistical significance. We used blinded video assessments to control bias because we felt it was inappropriate to administer a traditional placebo to OMD subjects given that their symptoms are so disabling, limiting ability to eat and speak. One reason the change in severity on blinded assessments did not reach statistical significance may be that the video assessments did not demonstrate the severity of the OMD as clearly as direct in person examination. Further, training raters for video assessments would be paramount in recognition of the symptoms of OMD in future research. In a prior study that scored the severity of OMD, it was shown that the severity of OMD is often underestimated by video assessment [32]. A post hoc analysis of variance in this study showed the baseline score for GDS for the blinded raters in this study was nearly 2 points lower than the unblinded rater who examined the patients face to face, demonstrating a significant difference in severity assessment by video versus in person exam ($p = 0.01$). This difference and associated standard deviation may explain why a significant difference in video assessment severity scores could not be detected. It would seem that blinded video ratings as a primary endpoint may not be the correct assessment for future OMD trials, most likely because the dystonic jaw or tongue muscle activity is not always accompanied by overtly visible abnormal jaw or tongue movements. There are also biases inherent in unblinded evaluation as well. The questions that arise then are how to design an appropriate trial for the next phase of clinical trials that would maintain control and how best to appreciate the change in severity. Design options could include a delayed start trial design such that patients receive either toxin or placebo at baseline, then the alternate at 6 weeks. The benefit of this delayed start for patients that initially receive placebo is that they would not be required to wait 12 weeks until receiving therapy. In this design, the injector could also be blinded and able to do in person severity assessments. Another option may be to evaluate different doses, using minimally effective dose versus higher traditionally effective doses. Regarding endpoints, since there is no validated rating scale for OMD [16, 33], using a patient-related quality-of-life measure would be an appropriate approach. Several studies have shown that QoL improves with toxin treatment of OMD [13, 14]. The OMDQ-25 is a validated instrument that has been shown by us and others to demonstrate response [12, 34].

Several clinical findings in this study are of interest for the evaluation and treatment of this complex disorder. Six patients had combined jaw-opening and -closing dystonia with 5 of these having spasmodic movements in both directions and 1 with a tremor. In published reviews, patients are generally classified as either jaw-opening, -closing, or deviation [1, 3, 31]. Our series demonstrates that movements in OMD can include various combinations of these movements, a finding that is not surprising considering that dystonia often includes simultaneous contraction of agonists and antagonists. This is similar to bidirectional cervical dystonia that has been observed [35]. The dosing scheme we developed was from experience with Asians who had X-linked dystonia parkinsonism [11]. It would seem those doses were too high for idiopathic and tardive OMD. We found adverse events in 50% of patients at the lower end of the dosing spectrum used in this population, while the rate in X-Linked dystonia parkinsonism was 13–19% depending on the muscles injected [11]. While dystonia is traditionally thought of as a single neurologic disorder, it is likely comprised of different diseases modulating

clinical symptoms through varied pathways. Therefore, it is possible that 1 cannot use a universal dosing guide for all causes of OMD. Further, the dose of aboBoNTA for genioglossus, which was initially set at twice the dose of onabotulinumtoxinA previously received, was too high. The appropriate ratio is closer to 1:1. It is possible the ratio recommended of 2 to 3 to 1 aboBoNTA versus onabotulinumtoxinA for cervical dystonia is not appropriate for all disorders or muscle groups [36]. Further work is needed on devising appropriate dosing and dosing ratios of different toxin types for OMD. Our dose finding study in this indication was too limited to test the optimal dose in OMD.

aboBoNTA was generally well tolerated in this study, though the occurrence of dysphagia led us to modify the genioglossus dose. It seems injections of this muscle were mostly responsible for dysphagia, although medial pterygoid injections may also play a role. Lowering the dose resulted in less dysphagia in the final 8 cases. Toxin spread may be another issue to address in relation to aboBoNTA in the cranial region. Molecular weight and presence of complexing proteins do not seem to affect diffusion or spread of toxin, suggesting that aboBoNTA should not have different spread than other toxin types. However, injection volume and dilution have been shown to be factors in spread and should be considered when injecting muscles in the cranial region [37, 38]. Though some providers may be uncomfortable injecting the genioglossus muscle, it is easy to localize using a submandibular approach with EMG guidance and an important target for OMD treatment when the tongue is involved [4]. Prevention of adverse effects involves the accurate injection into the selected muscles using EMG guidance and appropriate dosing. Substantial benefit and fewer adverse effects can be achieved by injection limited to the most affected muscles [16].

Conclusions

These results suggest that dose patterns individually adapted to match the nature of abnormal movements can be effective in OMD with limited side effects. Further, among the multiple outcome measures evaluated, QoL appears to be a more sensitive measure than video-based ratings. Adaptive clinical trial design may be useful in future clinical trials to limit ethical constraints of placebo injections in the treatment of this particularly disabling form of dystonia. Further research in the use of aboBoNTA for OMD is warranted as results of our pilot study indicate this therapy significantly improved QoL for patients with OMD.

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