AbobotulinumtoxinA for Equinus Foot Deformity in Cerebral Palsy: A Randomized Controlled Trial

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BACKGROUND: Although botulinum toxin is a well-established treatment of focal spasticity in cerebral palsy, most trials have been small, and few have simultaneously assessed measures of muscle tone and clinical benefit.

METHODS: Global, randomized, controlled study to assess the efficacy and safety of abobotulinumtoxinA versus placebo in cerebral palsy children with dynamic equinus foot deformity. Patients were randomized (1:1:1) to abobotulinumtoxinA 10 U/kg/leg, 15 U/kg/leg, or placebo injections into the gastrocnemius-soleus complex (1 or both legs injected). In the primary hierarchical analysis, demonstration of benefit for each dose required superiority to placebo on the primary (change in Modified Ashworth Scale from baseline to week 4) and first key secondary (Physician's Global Assessment at week 4) end points.

RESULTS: Two hundred and forty-one patients were randomized, and 226 completed the study; the intention to treat population included 235 patients (98%). At week 4, Modified Ashworth Scale scores significantly improved with abobotulinumtoxinA; mean (95% confidence interval) treatment differences versus placebo were –0.49 (–0.75 to –0.23; P = .0002) for 15 U/kg/leg and –0.38 (–0.64 to –0.13; P = .003) for 10 U/kg/leg. The Physician's Global Assessment treatment differences versus placebo of 0.77 (0.45 to 1.10) for 15 U/kg/leg and 0.82 (0.50 to 1.14) for 10 U/kg/leg were also significant (both Ps < .0001). The most common treatment-related adverse event was muscular weakness (10 U/Kg/leg = 2; placebo = 1).

CONCLUSIONS: AbobotulinumtoxinA improves muscle tone in children with dynamic equinus resulting in an improved overall clinical impression and is well tolerated.

WHAT'S KNOWN ON THIS SUBJECT:
- Chemodenervation with botulinum toxin is an effective treatment of the reduction of muscle hypertonia in children with dynamic equinus.

WHAT THIS STUDY ADDS:
- Despite its long history of use, this large-scale, randomized, placebo-controlled study fills an important evidence gap by prospectively demonstrating the efficacy of botulinum toxin in reducing muscle tone and spasticity and showing how this directly translates into meaningful functional improvement.

Dr Delgado participated in the conceptualization and design of the study, coordinated and supervised data collection at his site, participated in data interpretation, and drafted the initial manuscript; Drs Tilton and Russman participated in the conceptualization and design of the study, coordinated and supervised data collection at their sites, participated in data interpretation, and critically reviewed the manuscript; Drs Benavides, Bonikowski, Carranza, Dabrowski, Dursun, Gormley, Jozwiak, Matthews, Maciag-Tymecka, and Unlu coordinated and supervised data collection at their sites, participated in data interpretation, and critically reviewed the manuscript.
Cerebral palsy (CP) is the most common cause of chronic motor disability in childhood.1–3 Paresis and spasticity, resulting from the upper motor neuron lesion, are significant contributors to the motor deficit and can result in the development of joint contractures, which initially are dynamic but, if left untreated, can become fixed joint deformities. Equinus is the most common foot deformity and is often associated with spasticity in the gastrosoleus muscle complex (GSC).4 Treatment aims to reduce excessive plantarflexion, thereby improving gait and motor function.

The introduction of botulinum neurotoxin type-A (BoNT-A) as a treatment of spasticity in the 1990s5 represented a major advance in the management of CP and has led to a reduced need for orthopedic surgery.6 Clinical guidelines now recommend that BoNT-A should be offered as an effective and generally safe treatment of localized/segmental spasticity in children and adolescents with CP.7,8 Such guidelines are based on data from several studies assessing either single or repeat dosing of BoNT-A in the pediatric CP population. However, thus far, studies have been of variable quality, and there have been few Class I studies. Moreover, at the time of publishing, the US Food and Drug Administration has not approved the use of BoNT-A for pediatric use in the United States. This was the first large-scale, international, randomized, placebo-controlled study designed to prospectively assess the efficacy and safety of 1 BoNT-A formulation, abobotulinumtoxinA (Dysport, Ipsen Pharma, Wrexham, UK), compared with placebo in children with spasticity associated with CP. Unlike previous studies that have tended to focus on specific aspects of spasticity (eg, range of motion or gait), this study aimed to demonstrate efficacy by using a variety of clinical and functional outcome measures and show how reductions in muscle tone and spasticity translate into improvements that are of direct relevance to patients and their families.

METHODS
This was a phase III, international, multicenter, double-blind, prospective, randomized, placebo-controlled, single-dose study (clinicaltrials.gov identifier NCT01249417). Institutional review boards at the participating sites approved the protocol, and the trial was executed in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice Guidelines.

Patients
Children (aged 2–17 years) with a diagnosis of spastic hemiparesis, paraparesis, diparesis, or tetraparesis due to CP9 were recruited from 23 outpatient centers (6 countries) specialized in the management of children with CP. Patients had to be ambulatory, with or without walking aids, have a Gross Motor Function Classification System (GMFCS) Level of I through III, and show an equinus foot positioning during the stance phase of the gait. Patients also had to have a Modified Ashworth Scale (MAS)10 score ≥2 and a spasticity grade (Y) of 2 to 4 on the Tardieu Scale11 (with a spasticity angle [X] of ≥10°) at the ankle joint of the (most) affected limb to be injected. Patients could be BoNT-naive or previously treated, but the last BoNT injection for any condition must have been >6 months before study entry. An established physiotherapy and/or orthotic regimen was permitted provided that it had begun >1 month before study start and was maintained throughout the study.

Exclusion criteria included nonambulatory status, a fixed myocontracture (defined by a passive range of motion angle by the Tardieu Scale [X₀,Y] of ≤80° in ankle dorsiflexion), severe athetoid/dystonic movements in the targeted leg(s), a significant leg length difference (>2 cm), treatment with any drug that interferes with neuromuscular function (eg, aminoglycoside antibiotics or neuroblocking agents used during surgery) ≤30 days before study treatment, or any other medical condition, laboratory, or diagnostic procedure finding that might preclude administration of abobotulinumtoxinA. Patients with known resistance or sensitivity to BoNT or any of the components in the abobotulinumtoxinA formulation were also excluded from the study. In addition, patients were excluded if they had any previous surgery for lower limb spasticity or previous injections with alcohol and/or phenol or serial casting within the previous 12 weeks.

Study Medication, Randomization, and Blinding
Eligible patients were randomized using the sponsor’s computer-generated scheme in a ratio of 1:1:1 to abobotulinumtoxinA 10 U/kg/leg (ie, 20 U/kg for bilateral injections), abobotulinumtoxinA 15 U/kg/leg (ie, 30 U/kg for bilateral injections), or placebo and were stratified according to age (2–9 and 10–17 years) and BoNT-naive or nonnaive status as assessed at baseline. Doses were chosen on the basis of previous clinical studies12,13 and are specific to abobotulinumtoxinA. Because of proprietary differences in manufacturing and assay procedures, potency units for abobotulinumtoxinA are not interchangeable with other BoNT-A products.14

AbobotulinumtoxinA and placebo were provided as a white lyophilized
assessments of MAS of the GSC. The same investigators performed the Global Assessment (PGA) and goal attainment scaling (GAS). The Global Assessment Scale at each visit. A separate and blinded investigator to the MAS score performed the PGA of treatment response since the injection using a 9-point scale from −4 (markedly worse) to 4 (markedly improved). GAS was assessed using a list of preselected goals specifically defined for this population. Full details of PGA and GAS are given in the Supplemental Data.

Treatment-emergent adverse events (TEAEs) and vital signs were recorded at each visit.

Statistical Analysis
The primary efficacy end point was the change from baseline to week 4 in the derived MAS score in the GSC at the ankle joint of the (most) affected leg and was analyzed using an analysis of covariance model with baseline MAS, BoNT-naive or nonnaive status, age, and center included as covariates.

The first key secondary end point was mean PGA, and the second secondary end point was mean GAS T scores at week 4 (GAS T scores represent a derived statistic in which scores are standardized to allow comparison between individuals; a T score of ≥50 represents goals achieved as expected or better than expected). Both secondary efficacy measures were analyzed by using an analysis of variance model using the same covariates as included for the primary efficacy end point. Week 4 Tardieu Scale scores (X_{V1}, X_{V3}, Y, and X), mean change from baseline to week 12 in derived MAS scores, and mean PGA scores at week 12 were included as tertiary end points.

Efficacy and safety analyses were performed on the intention-to-treat population including all randomized participants who received at least 1 injection of study treatment in the GSC and had recorded MAS scores at baseline and week 4. A 4-step hierarchical method for the primary and first secondary efficacy end points was predefined to control the family-wise type I error rate of 0.05. Each step had to be considered significant for testing of the next hierarchical step. Step 1 assessed the superiority of the 15 U/kg/leg dose versus placebo on the primary efficacy end point, step 2 assessed the superiority of the 15 U/kg/leg dose versus placebo on the secondary efficacy end point, step 3 assessed the 10 U/kg/leg dose versus placebo on the primary efficacy end point, and step 4 assessed the superiority of the 10 U/kg/leg dose versus placebo on the secondary efficacy end point. The second secondary efficacy end point and tertiary end points were compared at a 0.05 type I error rate (without adjustment).

Sample Size Calculation
A total of 76 patients per arm were estimated to provide 85% power at the 5% significance level to detect a significant effect of either active dose versus placebo for the primary and 90% power for the first secondary efficacy end point. This calculation assumed a 3% dropout rate at week 4 and mean (SD) changes from baseline to week 4 in the derived MAS score of −1.3 (0.8) and −0.9 (0.8) in the abobotulinumtoxinA and placebo groups, respectively.

RESULTS

Subject Disposition and Baseline Characteristics
The study started on July 5, 2011, and completed on June 25, 2014. Overall 253 patients were screened; of these, 241 were randomized, 226 completed the study, and 15 prematurely terminated (Fig 1). Only 1 patient in the placebo group and none from the abobotulinumtoxinA groups withdrew from the study because of an adverse event. Two
patients, who were screening failures, were erroneously randomized to the placebo group and were withdrawn before receiving study treatment. The intention-to-treat population included 235 patients (98%). Table 1 shows the baseline characteristics per treatment group.
51.5 [1.3] for abobotulinumtoxinA 10 U/kg/leg), patients in the placebo group did not reach the expected level (score 46.2 [1.3]). The adjusted mean (95% CI) treatment differences of 4.65 (1.59 to 7.71) for the abobotulinumtoxinA 15 U/kg/leg group and 5.32 (2.31 to 8.32) for the abobotulinumtoxinA 10 U/kg/leg group were significant versus placebo \((P = .003\) and \(P < .001\), respectively).

**Tardieu Scale**

Both doses improved the Tardieu Scale spasticity grade Y at 4 weeks. For the 15 U/kg/leg dose, week 4 improvements were also accompanied by significant improvements in the angle of catch \(X_{V3}\) and angle of arrest \(X_{V1}\) (Table 3). Although the 10 U/kg/leg dose showed positive tendencies on these angles, changes were not significant.

**Safety and Tolerability**

Most patients in the abobotulinumtoxinA groups tolerated treatment. During the study, 144 subjects reported at least 1 TEAE, of which most were of mild intensity. In all groups, the most frequently reported TEAEs were upper respiratory tract infection. The incidence of treatment-related TEAEs was low in all 3 groups; only 2 treatment-related TEAEs were reported by >2% of subjects in any treatment group: pyrexia and local muscular weakness (Table 4). Two patients in the abobotulinumtoxinA 10 U/kg/leg, 3 patients in the abobotulinumtoxinA 15 U/kg/leg, and none in the placebo group had a TEAE of epilepsy (all considered unrelated to treatment). Of the 5 reported cases, only 1 was a new occurrence of epilepsy (in the 10 U/kg/leg group); the other 4 cases all had a previous history of seizures. Five subjects experienced serious TEAEs; 4 of these subjects were in the placebo group (upper limb fracture, pneumonia and rotavirus infection, head injury, and gastroenteritis), and the other subject was in the abobotulinumtoxinA 10 U/kg/leg group (adenoid hypertrophy).
All of the serious TEAEs were unrelated to study treatment.

**DISCUSSION**

Despite its long history of use, this is the first prospective study to demonstrate the efficacy of a BoNT-A product in reducing muscle tone and spasticity and improving function when injected for the treatment of dynamic equinus foot deformity. All steps in the predefined hierarchical analysis of MAS and PGA were positive, and the study met both the primary and secondary objectives.

Previous studies have generally been small, focused on motor aspects of spasticity, and/or have not consistently used standardized methods of assessment. Since these early studies, it has become increasingly understood that definitions of treatment success should go beyond muscle relaxation and also consider the consequences of treatment on patient function.

The robust quality and breadth of information provided by this study therefore fills an important evidence gap.

AbobotulinumtoxinA 10 U/kg/leg and 15 U/kg/leg produced significant reductions in muscle tone in the intention-to-treat population compared with placebo. These improvements in MAS scores remained significant at week 12.

TABLE 3 Tardieu Scale at Week 4: Adjusted Change From Baseline to Week 4 in Tardieu Scale Scores (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 78)</th>
<th>ABO 10 U/kg/leg (n = 79)</th>
<th>Treatment Effect: ABO 15 U/kg/leg (n = 79)</th>
<th>Treatment Effect: ABO 15 U/kg/leg (n = 79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angle of arrest (XIV1)</td>
<td>−1.2 (−3.9 to 1.5)</td>
<td>0.6 (−2.1 to 3.2)</td>
<td>1.8 (−1.4 to 4.9), P = 0.27</td>
<td>2.9 (0.3 to 5.5), P = 0.10</td>
</tr>
<tr>
<td>Angle of catch at fast speed (XIV2)</td>
<td>3.6 (0.3 to 6.8)</td>
<td>6.8 (3.6 to 9.9)</td>
<td>3.2 (−0.6 to 7.0), P = 0.10</td>
<td>10.9 (7.8 to 14.1), P = 0.0003</td>
</tr>
<tr>
<td>Spasticity grade (Y)</td>
<td>−5.4 (−7.7 to −3.0)</td>
<td>−7.0 (−9.2 to −4.7)</td>
<td>−1.6 (−4.4 to 1.2), P = 0.26</td>
<td>−7.8 (−10.1 to −5.5), P = 0.09</td>
</tr>
<tr>
<td>Spasticity grade (Y)</td>
<td>0.0 (−0.1 to 0.2)</td>
<td>−0.4 (−0.5 to −0.3)</td>
<td>−0.4 (−0.6 to −0.3), P &lt; 0.001</td>
<td>−0.4 (−0.6 to −0.3), P &lt; 0.001</td>
</tr>
</tbody>
</table>

Adjusted means were obtained from an analysis of covariance on the change from baseline with treatment, baseline score, age range at baseline, BoNT status at baseline, and center as covariates. ABO, abobotulinumtoxinA.

TABLE 4 Treatment-Related AEs

<table>
<thead>
<tr>
<th>Preferred Term, n (%)</th>
<th>Placebo (n = 79)</th>
<th>ABO 10 U/kg/leg (n = 80)</th>
<th>ABO 15 U/kg/leg (n = 80)</th>
<th>Total ABO (n = 160)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any treatment-related AE</td>
<td>7 (9)</td>
<td>6 (8)</td>
<td>5 (6)</td>
<td>11 (7)</td>
</tr>
<tr>
<td>Muscular weakness</td>
<td>1 (1)</td>
<td>2 (3)</td>
<td>0</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Choking</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Piloerection</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
<td>1 (1)</td>
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<tr>
<td>Arthralgia</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
<td>1 (1)</td>
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<tr>
<td>Pyrexia</td>
<td>2 (5)</td>
<td>1 (1)</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>0</td>
<td>1 (1)</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>0</td>
<td>1 (1)</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Facal incontinence</td>
<td>0</td>
<td>1 (1)</td>
<td>0</td>
<td>1 (1)</td>
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<tr>
<td>Injection site erythema</td>
<td>0</td>
<td>1 (1)</td>
<td>0</td>
<td>1 (1)</td>
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<tr>
<td>Injection site reaction</td>
<td>0</td>
<td>1 (1)</td>
<td>0</td>
<td>1 (1)</td>
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<tr>
<td>Injection site rash</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Pain in extremity</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Conjunctival irritation</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

ABO, abobotulinumtoxinA; AE, adverse event.

Although the study was not designed to directly compare the efficacy of the 2 active treatment groups, it is of note that the higher dose produced a slightly greater improvement in muscle tone (MAS scores) than the lower dose at weeks 4 and 12.

Although use of the MAS is standard practice when assessing interventions for spasticity, many now argue that the MAS is best described as an assessment of muscle tone or muscle resistance to passive muscle stretch and that scales such as the Tardieu Scale are better measures of spasticity because of the ability to assess resistance to stretch at 2 (well-defined) speeds, being more consistent with the definition of spasticity. In this phase III study, MAS was chosen as the primary outcome measure for consistency with other studies conducted in this field. To the best of our knowledge, ours is the only pediatric randomized controlled trial to use both the MAS and the Tardieu Scale simultaneously, and our findings suggest that XV3 (angle of catch – fast speed) assessment is more sensitive to treatment-induced changes in spasticity and allows the quantification of improvement. The increase in XV3 in ankle plantarflexors was 6.8° in the 10 U/kg/leg group and 10.9° in the 15 U/kg/leg group. As such, we agree with recommendations to use more than just the MAS in the assessment of spasticity and confirm the utility of these early studies, it has become increasingly understood that definitions of treatment success should go beyond muscle relaxation and also consider the consequences of treatment on patient function.
of the Tardieu Scale in pediatric clinical assessment of spasticity. Improvements in muscle tone at both abobotulinumtoxinA doses at week 4 were also associated with a significant overall clinical improvement based on the PGA, and PGA scores were still highly significant at week 12 indicating a carryover of benefit beyond the duration of BoNT-A action. The results of the PGA confirm that the treating investigators were able to observe clinically meaningful improvements in their patients (beyond specific assessments of muscle status). The inclusion of PGA as a component of the hierarchical efficacy analysis was a key feature of the study because most previous studies have not attempted to directly link improvements in motor status to improvements in overall function.

The use of GAS was another defining feature of the study, and the results clearly demonstrate that improvements in tone and spasticity allow the patients to achieve their functional goals of having a better gait pattern and other important daily activities. Such holistic assessments of function and well-being are in line with what is actually done in best clinical practice and provide a pragmatic and consistent way of determining the true clinical effectiveness of an intervention (taking both efficacy and tolerability into account). Moreover, in our experience, use of goal setting enables effective discussions between the treating physician and the patient and family regarding realistic expectations of treatment.

Both doses of abobotulinumtoxinA were well tolerated, and there was no evidence of a dose relationship for adverse events. The most frequent TEAEs were common childhood infections (upper respiratory tract infections), and the reports of pyrexia and muscular weakness were in line with previous studies. Five patients in the abobotulinumtoxinA groups had an AE of epilepsy recorded versus none in the placebo group; however, none were considered related to study treatment, and there was an overrepresentation of epilepsy in the treatment groups.

Strengths of the study included the hierarchical approach to testing that required superiority on measures of muscle tone and clinical benefit. The 15 U/kg/leg dose was tested first because this dose is approved in several countries. The study was not designed to compare between dose levels because, in clinical practice, physicians require dosing flexibility to meet individual patient clinical needs and goals. We have shown that both doses are efficacious in managing children with dynamic equinus foot deformity (thereby allowing dose adjustment according to clinical presentation). Another strength was significant training given to injectors. To ensure a standardized technique, investigators were shown how and where to inject using guidance techniques to improve localization. To improve the reliability in using different assessments (MAS/Tardieu/range of motion), investigators were trained (via lectures, manuals, and hands-on training) and certified on the use of the scales. For example, when assessing muscle tone and spasticity, investigators were trained on how to position and distract the patient, how to grip on patient’s proximal and distal limb segments, how to accurately determine joint angles, and how to interpret the scales. The joint movement velocity was standardized by training the investigators on how to move the joint from maximum flexion to maximum extension using consistent speeds (eg, 1 second while saying “one thousand one” for the MAS; <1 second saying “one” for the Xy3 in the Tardieu Scale). Study limitations include the lack of patients with severe CP (Gross Motor Function Classification System Levels IV–V) who were excluded as this study was designed for ambulatory children. This study only assessed the efficacy of a single injection cycle; further assessments in the long-term open-label extension study will provide better insights into the long-term efficacy of repeated injections.

CONCLUSIONS
The results of this study clearly show that single injections of both abobotulinumtoxinA doses (10 and 15 U/kg for unilateral injections, 20 and 30 U/kg for bilateral injections) significantly reduce muscle hypertonia and spasticity translating into clinical and functional benefits and are well tolerated in pediatric patients with CP.

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ABBREVIATIONS
BoNT-A: botulinum neurotoxin-A
CI: confidence interval
CP: cerebral palsy
GAS: goal attainment scaling
GSC: gastrosoleus muscle complex
MAS: Modified Ashworth Scale
PGA: Physician’s Global Assessment
TEAE: treatment-emergent adverse event
REFERENCES


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