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Clinical Observations

AbobotulinumtoxinA Efficacy and Safety in Children With Equinus Foot Previously Treated With Botulinum Toxin

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ABSTRACT

Background: The effects of botulinum toxin are transient, and repeat injections are required in children with lower-limb spasticity. However, the efficacy of botulinum toxin in patients who have received previous injections has remained largely unexplored.
Methods: We present subgroup analyses of a phase III study conducted in ambulatory children (aged two to 17) with spastic equinus foot. Patients were randomized to single doses of abobotulinumtoxinA 10 U/kg/leg, 15 U/kg/leg, or placebo injected into the gastrocnemius-soleus complex (one or both legs). The first analysis was prespecified to review the effect of abobotulinumtoxinA in children previously treated with botulinum toxin versus those children new to the treatment; a second *post hoc* analysis evaluated the effect of abobotulinumtoxinA in children who changed botulinum toxin formulation.
Results: Of the 241 randomized patients, 113 had previously received botulinum toxin, including 86 who had been treated with another formulation. In both analyses, muscle tone (Modified Ashworth Scale) and the Physicians Global Assessment, at week 4, improved with abobotulinumtoxinA treatment versus placebo, regardless of baseline botulinum toxin status. Placebo responses in patients new to treatment were consistently higher than in the previously treated group.
Conclusions: These results demonstrate similar abobotulinumtoxinA efficacy and safety profiles in children with spasticity who are new to botulinum toxin treatment and those children who were previously treated. The efficacy and safety of abobotulinumtoxinA treatment in these previously treated patients were comparable with the overall trial population, indicating that doses of 10 and 15 U/kg/leg are suitable starting doses for children with spasticity regardless of the previous botulinum toxin preparation used.

Introduction

Although cerebral palsy is considered a nonprogressive disorder in terms of the underlying brain damage,[1] the development of spasticity and other features of the upper motor neuron syndrome often cause developmental disabilities. In a growing child, these can frequently result in physical deformities, activity limitation, and participation restriction that, without proper management, may worsen over time and continue well into adulthood.[2] Chemodenervation with botulinum toxin type A is an established method of reducing spasticity in children with cerebral palsy.[3-5]

The physiological effect of botulinum toxin type A on nerve terminals can be detected within two to three days after injection and continues for several weeks after injection.[6] The prescribing information for all botulinum toxin type A products mandate at least a 12-week interval between injections, although recent analyses with abobotulinumtoxinA (Dysport; Ipsen Pharma, Wrexham, UK) indicate that for some children the time to retreatment (i.e. duration of therapeutic efficacy) can be longer.[7] Nevertheless, since the effect is temporary, injections need to be repeated to achieve long-lasting efficacy and to manage the changing needs of children as they grow and develop.[3] Despite this clinical need, the efficacy of botulinum toxin type A injections in patients who have received previous injections has remained largely unexplored. Furthermore, there has been few literature published on the efficacy of botulinum toxin type A treatment when changing from one formulation to another,

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which is an important question for patients considering a change in their treatment.

We have previously reported the results of a large, prospective, international, randomized, placebo-controlled, double-blind study designed to prospectively assess the efficacy and safety of abobotulinumtoxinA versus placebo in children with dynamic equinus foot deformity due to cerebral palsy.[8] In this study, patients were stratified at randomization according to age and previous exposure to botulinum toxin (including botulinum toxin type A and type B) treatment. Here, we report the results of a preplanned subgroup analysis comparing the efficacy and safety of abobotulinumtoxinA in patients who had previously been treated with botulinum toxin before study entry compared with those patients who were new to treatment. In addition, to provide information on efficacy of botulinum toxin type A when changing formulations, we also performed an exploratory *post hoc* analysis to determine the efficacy and safety of abobotulinumtoxinA in patients previously treated with onabotulinumtoxinA (Botox; Allergan, Inc, Irvine, CA, USA) or incobotulinumtoxinA (Xeomin; Merz Pharmaceuticals GmbH, Frankfurt, Germany) compared with the overall population.

Methods

This was a double-blind, prospective, randomized, placebo-controlled, single-dose study (NCT01249417); the full details of which have been previously published.[8] 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 and procedures

In brief, this multicenter study included children (aged two to 17 years) with equinus foot positioning during stance phase of gait due to spastic cerebral palsy.[9] Patients were recruited from the study sites and were required to be ambulatory (Gross Motor Functional Classification System levels I-III), and had to have a derived Modified Ashworth Scale (MAS) score of greater than or equal to two and a spasticity grade (Y) of two to four on the Tardieu scale at the ankle joint of the (most) affected limb to be injected. Patients could be new to botulinum toxin treatment or could be previously treated, but the previous botulinum toxin injection for any condition must have been longer than six months before study entry. Key exclusion criteria were a nonambulatory status, a fixed ankle flexor myocontracture, severe athetoid or dystonic movements in the targeted leg(s), a significant leg length difference (more than 2 cm), and treatment with any medication that interferes with neuromuscular function 30 days or less before the study treatment. Patients were also excluded if they had previous surgery for lower-limb spasticity, previous injections with alcohol or phenol, or serial casting within the past 12 weeks.

Eligible patients were assessed at baseline and randomized in a ratio of 1:1:1 to a single treatment of 10 U/kg/leg abobotulinumtoxinA, 15 U/kg/leg abobotulinumtoxinA, or placebo into the gastrocnemius-soleus complex and were stratified by age (two to nine years and 10 to 17 years) and botulinum toxin status (i.e. patients new to botulinum toxin treatment and patients previously treated). Investigators and children and their families were blinded to treatment allocation, but investigators may have been aware of the treatment history. The primary outcome measure in the study was the change from baseline to week 4 in the MAS score, and the key secondary efficacy measure was the Physicians Global Assessment (PGA) of treatment response at week 4.

Preplanned subgroup analysis: Comparing treatment in patients new to botulinum toxin treatment with those previously treated

For the subgroup analyses, patients were categorized by their baseline botulinum toxin status (new to treatment or previously treated with any botulinum toxin formulation). Efficacy and safety analyses were performed on the intention-to-treat population, which included all randomized participants who received one or more injections of study treatment in the gastrocnemius-soleus complex and had recorded MAS scores at baseline and week 4. MAS and PGA scores were analyzed against the relevant placebo control using an analysis of covariance model, with baseline score, age, and center included as covariates.

Post hoc subgroup analysis: Patients previously treated with incobotulinumtoxinA or onabotulinumtoxinA

This analysis included all patients who had been previously treated with a botulinum toxin type A formulation other than abobotulinumtoxinA before baseline. Although there was no restriction on the formulation previously used, the reality of the study meant that this analysis looked at patients previously treated with onabotulinumtoxinA or incobotulinumtoxinA. MAS and PGA scores were again analyzed against the relevant placebo control using an analysis of covariance model, with baseline score, age, and center included as covariates. In addition, a descriptive responder analysis (no statistical tests were performed) evaluated the proportion of patients who achieved one or higher grade improvement in MAS score versus baseline.

Results

Baseline characteristics

Of the 241 randomized patients, 113 had received botulinum toxin treatment before entering the study. Of these 113 patients, 86 had been treated with another botulinum toxin type A formulation; 80 patients had previously received onabotulinumtoxinA (mean ± S.D., dose 207 ± 105 U) and six patients had previously received incobotulinumtoxinA (190 ± 73 U). Baseline characteristics for each of the subgroups are provided in the Table; there were similar proportions of males and females in each group, and there were no notable differences in the proportion of patients with each Gross Motor Functional Classification System level. As might be predicted, patients in the group new to botulinum toxin treatment were generally younger than those patients previously treated. One patient in the placebo group and none from the abobotulinumtoxinA groups withdrew from the study due to a treatment-emergent adverse event (TEAE).[8]

Efficacy outcomes

In the preplanned analysis, comparing patients new to botulinum toxin treatment with those patients previously treated with botulinum toxin, muscle tone (assessed by MAS) at week 4 improved with both doses of abobotulinumtoxinA treatment compared with placebo, regardless of baseline botulinum toxin status (Fig 1). Statistical significance versus the relevant placebo control was achieved for all comparisons, except for the 10 U/kg/leg abobotulinumtoxinA versus placebo in the new to botulinum toxin treatment group, where the placebo response was notably higher than the previously treated group. Likewise, the PGA of treatment response for all subgroups followed the same trend as seen for the overall trial population. Again, the placebo response for PGA in the new to botulinum toxin treatment group was higher than for those in the previously treated group.