An Overview of Clinical Trial Data on a New Formulation of Botulinum Neurotoxin Type A

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According to the American Society for Aesthetic Plastic Surgery, the number of aesthetic procedures involving botulinum neurotoxin type A (BoNT-A) increased 3681% between 1997 and 2008. Almost 2.5 million procedures were performed using this neurotoxin last year, accounting for approximately 25% of all nonsurgical aesthetic procedures performed in 2008.1 Both aesthetic and therapeutic uses of this neurotoxin are likely to increase in the coming years.

In 2009, a new US formulation of BoNT-A (BoNTA-ABO; Dysport [abobotulinumtoxinA]; Medicis Aesthetics, Scottsdale, AZ) was approved by the US Food and Drug Administration (FDA) for the treatment of moderate to severe glabellar lines. Key features of this new BoNT-A formulation are shown in the Table.2 Outside of North America, Dysport has been used for therapeutic applications since 1991 and for aesthetic applications since 2001. Before receiving FDA approval, BoNTA-ABO had been studied in the United States under the proposed trade name Reloxin. At the time of approval, the FDA required Medicis to retain the Dysport name.

Several reports of pivotal US trial data regarding the safety and efficacy of this agent in patients with moderate to severe glabellar lines have been published recently in major journals.3-7 This supplement provides an up-to-date and comprehensive overview of the safety, efficacy, immunogenicity, and manufacturing of this new US botulinum neurotoxin formulation.

**BOTULINUM NEUROTOXIN: NEW USES FOR AN OLD MOLECULE**

Food poisoning by *Clostridium botulinum* neurotoxin has probably been a cause of death since humans first began storing food.8 *C botulinum* is a Gram-positive, anaerobic bacteria that is categorized on the basis of the toxins it secretes. Of the eight known serotypes (A, B, C1, C2, D, E, F, and G), seven are neurotoxins that are synthesized as single polypeptide protoxins. Before secretion, the molecules are “nicked” by bacterial proteases to produce the active molecule. The neurotoxins bind to specific receptors at nerve terminals and inhibit the release of acetylcholine, resulting in muscle paralysis.9

Even the earliest reports of botulinum neurotoxin, such as an investigation of “sausage poison” by Kerner in the 1820s, recognized its possible therapeutic benefits. In his words, “[The toxin] could be of benefit in the many diseases which originate from hyperexcitation of this [autonomic nervous] system.”8 Over the last few decades, the focus on *C botulinum* neurotoxins has shifted from their poisonous nature to their therapeutic and aesthetic benefits.

The elucidation of the mechanism of action of botulinum neurotoxin in the years after World War II was driven primarily by concerns over its potential as a biologic weapon. Nevertheless, these studies ultimately led to explorations of potential therapeutic uses. In 1973, Scott et al10 showed that botulinum neurotoxin could be used to paralyze extraocular muscles in animals and suggested that this property made it a candidate for the treatment of strabismus and other muscle disorders.10 After many years of additional animal experiments, ultimately followed by clinical trials in humans, BoNT-A was approved by the FDA for the treatment of adult strabismus, blepharospasm, and hemifacial spasm under the trade name Oculinum. Shortly thereafter, Allergan (Irvine, CA) acquired the rights to this compound and changed the name to Botox.9,11 Approved therapeutic indications that have been added since the initial approval include cervical dystonia and hyperhidrosis.12 Investigational therapeutic uses include a wide array of muscle, pain, ophthalmic, and genitourinary disorders.11

In the 1990s, Jean and Alastair Carruthers noticed that patients who received botulinum neurotoxin treatments...
for moderate to severe glabellar lines.9,15 

Corrugator muscles (two 10-unit aliquots in each [medial and lateral]) and procerus muscle (one 10-unit aliquot)

No more than every three months

Hypersensitivity to any botulinum toxin product or excipients, allergy to cow’s milk protein, and infection at the proposed injection site(s)

Table. Characteristics of Dysport in the treatment of moderate to severe glabellar lines2

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Acetylcholine release inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose*</td>
<td>Total dose of 50 units given intramuscularly in five equal aliquots of 10 units each</td>
</tr>
<tr>
<td>Injection sites</td>
<td>Corrugator muscles (two 10-unit aliquots in each [medial and lateral]) and procerus muscle (one 10-unit aliquot)</td>
</tr>
<tr>
<td>Retreatment frequency</td>
<td>No more than every three months</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Hypersensitivity to any botulinum toxin product or excipients, allergy to cow’s milk protein, and infection at the proposed injection site(s)</td>
</tr>
<tr>
<td>Most common treatment-emergent adverse events (≥2%)</td>
<td>Nasopharyngitis, headache, injection site reaction, upper respiratory tract infection, eyelid edema, eyelid ptosis, sinusitis, and nausea</td>
</tr>
</tbody>
</table>

*Dose for treatment of moderate to severe glabellar lines. The potency units of Dysport are specific to the preparation and assay method used. They are not interchangeable with other preparations of botulinum toxin products, and therefore units of biologic activity of Dysport cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay method.

Although new to the United States, Dysport has been used for more than 15 years outside of this country and has been studied in more than 150 clinical trials. It is approved in 73 countries for therapeutic indications and in 27 countries for aesthetic uses. This extensive body of experience provides an important backdrop to the studies discussed in this supplement.

The comprehensive testing that has been conducted on this product for the treatment of glabellar lines exceeds the scope of testing performed on any botulinum neurotoxin products to date. Five multicenter phase III studies were conducted; three of these were randomized, placebo-controlled, double-blind trials and two were open-label studies, including one extension trial to evaluate long-term safety. Two of the placebo-controlled, double-blind studies involved fixed doses of BoNTA-ABO, while the third allowed variable dosing based on muscle mass and gender to reflect the current standard clinical practice of adjusting doses to meet an individual patient’s needs. Both single and repeated dosing (up to nine treatments) were assessed. Overall, 3574 patients received treatment with this recently approved agent during these trials.

The articles in this supplement present a comprehensive summary of clinical experience with this new US formulation of botulinum neurotoxin. For pharmaceutical substances intended for aesthetic use, safety is a primary concern. Rubin et al summarize safety data from the five phase III clinical trials of BoNTA-ABO. The product was well tolerated, with a safety profile comparable to placebo in terms of type, frequency, severity, and relatedness of adverse events. In addition, no cumulative safety issues were observed in repeat-dose studies. Efficacy data from the five phase III clinical trials are reported by Baumann et al. Both fixed (50-unit) and variable (50 to 80 units based on gender and muscle mass) dosing significantly improved glabellar lines compared with placebo (P < .001 for both analyses), and efficacy was maintained during multiple treatment cycles. Because repeated botulinum neurotoxin administration is usually required to maintain the desired aesthetic effect, the immunogenicity of these preparations is an important consideration. As described by Moy and Lawrence, no neutralizing antibodies were detected in 1554 patients who received at least one dose—and some up to nine doses—of BoNTA-ABO as determined by a radioimmunoprecipitation assay followed by a highly sensitive mouse protection assay. An interim analysis of an open-label extension study of patients who received retreatment with this agent provides additional support for the long-term safety of this formulation. Cohen et al report that no cumulative safety issues were noted and that the incidence of adverse events remained relatively constant or decreased with repeated treatment cycles. Pickett and Wortzman describe the mechanism of action of BoNTA-ABO and the production and purification process involved in its manufacture.

None of the studies discussed here or reported elsewhere involved a comparison between the two available botulinum neurotoxins (Dysport and Botox). Although these products differ in molecular weight, dosing, excipients, and toxin diffusion/migration characteristics,16,17 the potential impact of these differences on clinical outcomes has not been assessed.

Together, the articles presented in this supplement provide a thorough overview of the US clinical experience with this newly approved agent in the treatment of glabellar lines. In these large-scale phase III clinical trials, BoNTA-ABO resulted in safe, favorable, and reproducible outcomes. Both efficacy and safety were maintained with repeated treatments. On the basis of these data, we conclude that this product provides an important new option for the treatment of moderate to severe glabellar lines.
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REFERENCES


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