An Evaluation of Neutralizing Antibody Induction During Treatment of Glabellar Lines with a New US Formulation of Botulinum Neurotoxin Type A

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Background: The induction of neutralizing antibodies during the aesthetic application of botulinum neurotoxin type A is rare, but of potential clinical concern. Phase III studies of a new US formulation of botulinum neurotoxin type A, *Dysport* (BoNTA-ABO [abobotulinumtoxinA]; Medicis Aesthetics, Scottsdale, AZ), have not identified any cases of neutralizing antibody formation during the treatment of glabellar lines in patients who received up to nine treatments.

Objective: To provide an in-depth analysis of the potential for induction of neutralizing antibodies in the study population enrolled in phase III trials of BoNTA-ABO in the treatment of glabellar lines.

Methods: First and last available serum samples from patients in the BoNTA-ABO Glabellar Lines Development Program were screened for BoNTA-ABO antibodies with a radioimmunoprecipitation assay (RIPA), followed by a confirmatory competitive assay (RIPA-C). Confirmed RIPA-C–positive samples were further evaluated for the presence of neutralizing antibodies using a mouse protection assay (MPA), a highly specific bioassay for neutralizing antibodies. We conducted safety and efficacy evaluations, including day 30 responder rate (a rating of no or mild glabellar lines) and duration of response in the last treatment cycle.

Results: Of 1554 patients who received at least one BoNTA-ABO treatment (10 units at five injection points, for a total dose of 50 units/treatment; range one to nine treatments), five (0.32%) were antibody positive on the RIPA-C assay—two at baseline and three at the last treatment cycle. None of the RIPA-C–positive samples tested positive for neutralizing antibodies upon further evaluation using the highly specific MPA. Of note, the RIPA-C–positive group had a responder rate of 100% and a mean response of 103.3 days, while the RIPA-C–negative group had a responder rate of 90% and a mean response of 89.4 days. The safety of BoNTA-ABO did not appear to be altered in the RIPA-C–positive group.

Conclusions: At the dose and treatment interval used in the correction of glabellar lines, induction of neutralizing antibodies to BoNTA-ABO was not observed. None of the five samples that initially gave positive results in a RIPA-C assay were positive when further evaluated using the MPA. Clinically, RIPA-C–positive status did not correlate with any reduction in efficacy or an altered safety profile, although the small numbers prevent definitive conclusions. These data suggest that the five RIPA-C–positive samples represented false positives. *(Aesthetic Surg J 2009;29:S66–S71.)*

Botulinum neurotoxin type A (BoNT-A) injections are the most frequently sought nonsurgical aesthetic procedure, accounting for almost 2.5 million procedures in 2008 alone.[1] BoNT-A also has important therapeutic uses, including the treatment of movement disorders such as cervical dystonia and tremors. Both aesthetic and therapeutic uses of BoNT-A require repeated injections to maintain the desired effect(s). Accordingly, the potential of BoNT-A formulations for inducing neutralizing antibodies is of critical importance.

As with other antigens, BoNT-A immunogenicity is influenced by the specific formulation and by the extent of antigenic exposure, including specific activity, frequency of treatment, and dose.[2-5] The purity and

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specific activity of a formulation have been shown to have a significant effect on the induction of BoNT-A antibodies.[4,6] Preparations with a high specific activity require less protein per injection and therefore may reduce antigenic exposure and immunogenicity.[7] Frequent injections and long-term therapy increase a patient's total antigenic exposure and correlate with the appearance of BoNT-A–blocking antibodies.[5] Dosage is another important factor. One study found that only patients who received BoNT-A doses of more than 600 units for the treatment of movement disorders developed neutralizing antibodies.[2] The BoNT-A dose for aesthetic applications is much lower.

Antibody responses to currently available BoNT-A preparations are generally rare in patients undergoing treatment for movement disorders. Although the original formulation of a US Food and Drug Administration (FDA)–approved BoNT-A preparation (BoNTA-ONA [onabotulinumtoxinA]; Botox, Allergan, Irvine, CA) was associated with a neutralizing antibody rate of 9.5% in patients receiving large doses (mean dose of approximately 200 units per injection) for the treatment of cervical dystonia,[3] a revised BoNTA-ONA formulation introduced in the United States in 1998 was much less immunogenic. A study of 119 cervical dystonia patients did not identify any cases of blocking antibodies associated with the new formulation.[3] Recent studies suggest a neutralizing antibody rate of 1.2% in cervical dystonia patients treated with BoNTA-ONA for up to four years.[8]

In 2009, a new US formulation of BoNT-A, *Dysport* (BoNTA-ABO [abobotulinumtoxinA]; Medicis Aesthetics, Scottsdale, AZ), was approved by the FDA for the treatment of moderate to severe glabellar lines on the basis of data obtained from large-scale clinical trials. This formulation has been available in countries outside of North America since 1991. In a study conducted in Europe, Göschel et al[2] evaluated the immunogenicity of BoNTA-ABO and reported that in patients receiving the product for therapeutic purposes, the lowest dose that induced neutralizing antibodies was 15.5 ng (620 units).[2] None of the patients receiving lower doses developed neutralizing antibodies, while four of 40 (10%) patients receiving doses of more than 600 units had detectable titers of BoNT-A–neutralizing antibodies.

The induction of neutralizing antibodies to BoNT-A during aesthetic applications has not been systematically studied,[6] but is likely to be a very rare event because aesthetic procedures generally require much lower doses and longer retreatment intervals. Nevertheless, there has been at least one case report of a patient who developed neutralizing antibodies to BoNTA-ONA during the treatment of facial rhytides.[9] Such cases are of potential clinical concern.[9,10] Not only do they result in nonresponse to aesthetic treatment, but they may also prevent the future therapeutic use of BoNT-A in that patient.

Studies of BoNT-A–neutralizing antibodies are complicated by difficulty in detecting these antibodies.[6] The gold standard assay is the mouse protection assay (MPA), which tests for neutralizing BoNT-A antibodies by determining the ability of sera to prevent the death of mice given a lethal dose of botulinum toxin. Although this assay is highly specific (100%), it has low sensitivity (range 30%-50%).[11] Furthermore, because it relies on the use of live animals, both ethical and cost issues dictate against its use in large-scale antibody screening studies. Enzyme-linked immunosorbent assays, Western blots, and other rapid tests for antibody identification are less cumbersome than the MPA, but they detect both neutralizing and nonneutralizing antibodies and are therefore not as sensitive or specific.

As a key component of the BoNTA-ABO US Glabellar Lines Development Program, the immunogenicity of BoNTA-ABO during aesthetic applications has been closely evaluated. Individual phase III studies of BoNTA-ABO failed to identify any cases of neutralizing antibody formation during treatment of glabellar lines, but the methods used in these analyses have not been fully described.[12-14] Here we provide a comprehensive, in-depth evaluation of antibody formation in the study population enrolled in phase III trials of BoNTA-ABO for the treatment of glabellar lines. The data reported here indicate that patients treated with BoNTA-ABO did not develop neutralizing antibodies during the course of these studies at the prescribed dose and treatment schedules.

METHODS

The serum samples for antibody testing and the efficacy and safety data analyzed as part of this study were obtained from studies approved by the Institutional Review Boards of centers participating in a Glabellar Lines Development Program. These studies were conducted in accordance with ethical standards for biomedical research, as established by the 18th World Medical Assembly, Helsinki, Finland, 1946 and later revisions, and with US federal regulations and guidelines.

Patients and Treatment

The study population consisted of individuals enrolled in the BoNTA-ABO Glabellar Lines Development Program who had serum antibodies available for testing. Subjects provided written informed consent before enrolling in the original study. All patients in this study received at least one treatment consisting of 50 units of BoNTA-ABO (10 units/0.05 mL at each of five separate injection points in the glabellar region). Subsequent treatments (if any) were given approximately every 12 to 16 weeks, for up to nine retreatments.

Antibody Assessments

For each subject, the first and last available serum samples were analyzed for the presence of BoNTA-ABO antibodies as described below. All samples were analyzed at Ipsen Pharma AA, a subsidiary of Ipsen Biopharm, in Barcelona, Spain.

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