Antibody-induced secondary treatment failure in a patient treated with botulinum toxin type A for glabellar frown lines

Gabriele Stengel
Eva Kristina Bee
Hautarztpraxis Stengel and Bee, Münster, Germany

Abstract: Botulinum toxin type A (BTX-A) preparations are widely used nonsurgical treatments for facial wrinkles. Higher doses of BTX-A are also used for therapeutic purposes in the treatment of conditions involving increased muscle tone, such as cervical dystonia. The phenomenon of antibody-induced treatment failure is well known in the therapeutic setting, but reports are also emerging following cosmetic use of BTX-A. We describe the case of a 41-year-old female nurse who developed secondary treatment failure during 6 years of BTX-A treatment for glabellar lines. After a good response to the first BTX-A injection, the intensity and duration of effect decreased after subsequent treatments. Antibody tests revealed a high titer of neutralizing anti-BTX-A antibodies. This case shows secondary treatment failure due to the production of neutralizing antibodies following administration of BTX-A formulations for cosmetic purposes and demonstrates that immunogenicity of BTX-A preparations is an important consideration, even in the cosmetic setting.

Keywords: botulinum toxin type A, neutralizing antibodies, antibody-induced treatment failure

Introduction
Botulinum toxin type A (BTX-A) preparations are commonly used in therapeutic and cosmetic applications with great success. However, after initial good responses, therapy can subsequently fail either partially or completely (secondary therapy failure) due to a number of causes, including inadequate dosage, injection of inappropriate muscles, and development of BTX-A neutralizing antibodies. Antibody-induced treatment failure following treatment with BTX-A for therapeutic purposes has been reported to range from 4% to 10% of patients treated and to decrease to 1%–6% after the foreign protein load of the preparation used is reduced. The risk of developing antibody-induced treatment failure has been shown to increase with short injection intervals and high injected doses. Despite lower BTX-A dosages being used in cosmetic applications compared with therapeutics, there are now emerging reports of antibody-induced treatment failure in facial esthetics.

Case report
Here we report the case of a 41-year-old Caucasian woman who had been receiving BTX-A preparations for the treatment of glabellar lines for 6 years (Table 1). She was initially treated in 2004 with a commercially available BTX-A preparation, abobotulinumtoxinA (Dysport®, Ipsen Ltd, Slough, UK). The effects of treatment lasted for 3–4 months. However, following her next treatment with
From the beginning of 2009, we treated this patient with abobotulinumtoxinA in the glabellar region twice yearly and reported that the duration of effect subsequently diminished to a maximum effect of 3–4 weeks’ duration. From the beginning of 2009, we treated this patient with other BTX-A preparations, first with onabotulinumtoxinA (Botox®/Vistabel®, Allergan, Irvine, CA), and more recently with incobotulinumtoxinA (Xeomin®/Bocouture®, Merz Pharmaceuticals GmbH, Frankfurt, Germany). In December 2009, the patient’s serum was tested for the presence of neutralizing anti-BTX-A antibodies at a specialized laboratory (Toxogen GmbH, Hannover, Germany) using an in vitro mouse hemidiaphragm assay. The patient was positive for a high titer of neutralizing antibodies, suggesting that the cause of the secondary therapy failure experienced by this patient was neutralizing anti-BTX-A antibodies.

For this patient, switching to a botulinum toxin type B (BTX-B) preparation was not considered because the data show that BTX-B has a greater diffusion potential13 and a reduction in the protein load of BTX-A injections, for instance by using highly purified formulations,12 may be beneficial in limiting further esthetic use of BTX-A. Some clostridial complexing proteins have been found to enhance antibody production,11 and may therefore increase the risk of neutralizing anti-BTX-A antibodies. Indeed, reducing the foreign protein load of the early preparation of onabotulinumtoxinA decreased the risk of neutralizing anti-BTX-A antibodies.4 A further reduction in the protein load of BTX-A injections, for instance by using highly purified formulations,12 may be beneficial in patients receiving several cycles of BTX-A injections.

Therefore, we considered the possibility that the patient had neutralizing anti-BTX-A antibodies. This seemed likely since neutralizing anti-BTX-A antibodies would not be overcome by switching to another BTX-A formulation, and high antibody titers could prevent a response even to larger doses.

<table>
<thead>
<tr>
<th>Date</th>
<th>BTX-A preparation</th>
<th>Dosage</th>
<th>Area treated</th>
<th>Duration of effect</th>
<th>Approximate treatment interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>February 11, 2009</td>
<td>IncobotulinumtoxinA</td>
<td>28 U</td>
<td>Glabellar</td>
<td>First treatment: 12–16 weeks; Second treatment: maximum 8 weeks</td>
<td>6 months</td>
</tr>
<tr>
<td>February 25, 2009</td>
<td>OnabotulinumtoxinA</td>
<td>9 U</td>
<td>Glabellar, periorbital</td>
<td>2–3 weeks</td>
<td>1.5 months</td>
</tr>
<tr>
<td>May 28, 2009</td>
<td>OnabotulinumtoxinA</td>
<td>10 U</td>
<td>Glabellar, periorbital</td>
<td>2–3 weeks</td>
<td>3 months</td>
</tr>
<tr>
<td>August 26, 2009</td>
<td>IncobotulinumtoxinA</td>
<td>20 U</td>
<td>Glabellar, periorbital</td>
<td>3–4 weeks</td>
<td>3 months</td>
</tr>
<tr>
<td>December 24, 2009</td>
<td>IncobotulinumtoxinA</td>
<td>22 U</td>
<td>Glabellar, periorbital</td>
<td>3–4 weeks</td>
<td>4 months</td>
</tr>
<tr>
<td>January 19, 2010</td>
<td>IncobotulinumtoxinA</td>
<td>44 U</td>
<td>Glabellar, periorbital</td>
<td>3–4 weeks</td>
<td>1 month</td>
</tr>
</tbody>
</table>

Abbreviations: N/A, not available; BTX-A, botulinum toxin type A.

abobotulinumtoxinA in the glabellar region, the duration of effect was reduced to 8 weeks. From 2005 to 2008, prior to presentation at our clinic, the patient received further injections of abobotulinumtoxinA in the glabellar area twice yearly and reported that the duration of effect subsequently diminished to a maximum effect of 3–4 weeks’ duration.
highly-acidic pH,\textsuperscript{12} and therefore is associated with more side effects.\textsuperscript{12} Also, the duration of effect seen with BTX-B is not maintained for as long as that observed with BTX-A.\textsuperscript{14} Currently, there is no BTX-B preparation that is approved for esthetic indications,\textsuperscript{16} and the administration of BTX-A for cosmetic indications is not commonly used for this purpose.

Although initial reports stated that less than 1% of patients develop neutralizing anti-BTX-A antibodies in esthetics,\textsuperscript{15–17} this case, and others like it,\textsuperscript{8,9} highlight the fact that immunogenicity of BTX-As and neutralizing anti-BTX-A antibodies are still important issues. Indeed, recent reports monitored BTX-A neutralizing antibodies in patients receiving 1–10 cycles of BTX-A injections, with few patients achieving the maximum number of cycles.\textsuperscript{15–17} Therefore, the long-term effects of BTX-A on neutralizing anti-BTX-A antibody development still need to be investigated to estimate accurately the incidence and importance of neutralizing anti-BTX-A antibodies in esthetics. This is of particular significance given the widespread off-label use of BTX-A for cosmetic indications,\textsuperscript{18,19} and the administration of BTX-A preparations by nonmedically trained individuals.

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**References**


