Botulinum Toxin in Secondarily Nonresponsive Patients with Spasmodic Dysphonia

Niv Mor, MD¹,², Christopher Tang, MD²,³, and Andrew Blitzer, MD, DDS²,⁴,⁵

Abstract

Chemodenervation with botulinum toxin (BoNT) has been effective and well tolerated for all types of dystonia for >30 years. We reviewed outcomes of our patients treated with BoNT serotype A (BoNT-A) for spasmodic dysphonia (SD) who became secondarily nonresponsive. We found that 8 of 1400 patients became nonresponsive to BoNT-A (0.57%), which is lower than the secondary nonresponse rate in other dystonias. After a cessation period, 4 of our patients resumed BoNT-A injections, and recurrence of immunoresistance was not seen in any of them. When compared with patients with other dystonias, patients with SD receive extremely low doses of BoNT. Small antigen challenge may explain the lower rate of immunoresistance and long-lasting efficacy after BoNT-A is restarted among secondary nonresponsive patients with SD.

Keywords

botulinum toxin, Botox, onabotulinumtoxinA, spasmodic dysphonia, secondary nonresponse, immunoresistance

Results

In our cohort of 1400 patients, we identified 8 patients (6 women, 2 men) who became secondarily nonresponsive to onabotulinumtoxinA (Botox), a formulation of BoNT serotype A (BoNT-A). Suspected immunoresistance was confirmed with a single test dose of 5 U of BoNT-A to the frontalis muscle. Persistent frontalis muscle function indicated the presence of neutralizing antibodies. Patients with confirmed immunoresistance were offered rimabotulinumtoxinB (Myobloc), a formulation of BoNT serotype B. RimabotulinumtoxinB has a shorter duration of action, a more rapid return of symptoms, and a lower patient-reported performance as compared with onabotulinumtoxinA.¹⁰ Thus, after a washout period, patients were offered to either continue rimabotulinumtoxinB or restart onabotulinumtoxinA. Patients wishing to resume onabotulinumtoxinA were started at the previously effective dose, and adjustments were made according to each individual’s clinical response.
whom had adductor SD. All 4 were treated with bilateral electromyography-guided injection to the thyroarytenoid muscles. The washout period ranged from 6 to 121 months. Recurrence of the immune response was not seen in any of these patients. Currently, the duration of response after restarting onabotulinumtoxinA is 8.4, 20.3, 30.9, and 59.0 months. Data regarding injection dosage prior to developing immunoresistance were available in 3 of the 4 patients. Although statistical analysis was not performed because of the small sample size, patients who resumed onabotulinumtoxinA required a dose increase as compared with each patient’s previously effective dose (Table 1). The remaining 4 patients chose not to resume onabotulinumtoxinA but remained on rimabotulinumtoxinB. Of these patients, 3 had adductor SD, and 1 had abductor SD.

### Discussion

SD is a focal, speech-specific dystonia of the intrinsic laryngeal muscles, and BoNT is the mainstay of treatment. 11-13 With the increasing prevalence of long-term BoNT therapy, there have been concerns regarding its immunogenicity. 6-8,14-22 Eight of our patients with SD became secondarily nonresponsive to onabotulinumtoxinA (0.57%). During the washout period, all had a good clinical response to rimabotulinumtoxinB. Of the 4 patients who were restarted on onabotulinumtoxinA, all have responded well to re-injection, and thus far, none have demonstrated a return of the anamnestic immune response, with the longest duration of therapy currently at 59 months.

A prospective trial by Brin et al found that 4 of 326 patients (1.2%) with cervical dystonia developed immunoresistance to BoNT, which is twice the incidence of immunoresistance seen in our cohort. 7 Sankhla et al studied 7 patients who became secondarily nonresponsive to BoNT-A. 9 Six were treated for cervical dystonia and 1 for oromandibular dystonia. When compared with the patients of Brin et al and Sankhla et al, our patients tolerated BoNT-A injections for a longer duration before the becoming immunoresistant. Furthermore, our cohort received much smaller doses of BoNT (Table 2). Since the amount of antigen seen by a host has a direct affect on the magnitude of the immune response, it is possible that small antigen challenge is responsible for the lower nonresponse rate and longer latency period seen in our patients. 14-17,23

In the study by Sankhla et al, 9 all 7 patients tested positive for anti-BoNT-A antibodies. Six had reverted to negative antibody status after BoNT-A was discontinued, and all 6 showed a good clinical response once reinstating BoNT-A. However, 50% eventually reverted back to positive antibody status and were once again nonresponsive to BoNT-A. Unpublished data by Jankovic and Atassi, presented at Toxin 2015 in Lisbon, Portugal, indicate that within 6 to 12 months, the anamnestic immune response will eventually return in all patients with cervical dystonia who became secondarily nonresponsive to BoNT-A. 10 However, recidivism of the immunologic response was not observed in any of our patients. While this observation may be a result of the lower antigenic load seen in patients with SD, it is also possible that unknown immunologic factors are involved. For instance, it is plausible that the glottis itself is better able to tolerate foreign antigens and thus elicits a less robust immune response. 24-26

### Table 1. Spasmodic Dysphonia—Dosage and Duration in Current Study.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Cessation Period, mo</th>
<th>Postcessation Response to OnabotulinumtoxinA, mo</th>
<th>Precessation Dose, U</th>
<th>Postcessation Dose, U</th>
<th>Dose Increase, U</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>30.9</td>
<td>1.61</td>
<td>5.37</td>
<td>3.76</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>20.3</td>
<td>2.16</td>
<td>4.14</td>
<td>1.98</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>8.4</td>
<td>1.21</td>
<td>3.60</td>
<td>2.39</td>
</tr>
<tr>
<td>4</td>
<td>121</td>
<td>59.0</td>
<td>Unavailable</td>
<td>2.28</td>
<td>Unavailable</td>
</tr>
</tbody>
</table>

*aDosage calculated as mean units per side, per session, based on a 12-week session.*

### Table 2. Comparison of Spasmodic Dysphonia to Cervical and Oromandibular Dystonia.

<table>
<thead>
<tr>
<th>Treated Condition</th>
<th>Mean Dose, U</th>
<th>Mean Duration, mo</th>
<th>Sessions, n</th>
<th>Immunoresistance Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Our cohort SD</td>
<td>2.40 (0.91-4.14)</td>
<td>96 (15-179)</td>
<td>36</td>
<td>0.57</td>
</tr>
<tr>
<td>Brin et al CD</td>
<td>244</td>
<td>48</td>
<td>9</td>
<td>1.20</td>
</tr>
<tr>
<td>Sankhla et al CD</td>
<td>207 (50-400)</td>
<td>27 (15-43)</td>
<td>8</td>
<td>n/a</td>
</tr>
</tbody>
</table>

*Abbreviations: CD, cervical dystonia; n/a, not available; OD, oromandibular dystonia; SD, spasmodic dysphonia.*

*Ranges are cited in parentheses.*

*Dosage calculated as mean units per side, per session, based on a 12-week session.*
Conclusion

Immunoresistance to onabotulinumtoxinA in SD is uncommon. Current recommendations for the use of BoNT in patients who become secondarily nonresponsive allows for a 1-year washout period in the hopes that the patient will once again respond to therapy.27 In our practice, those who developed immunoresistance demonstrated a good clinical response to rimabotulinumtoxinB. Patients who ultimately resumed onabotulinumtoxinA were started at the previously effective dose, and adjustments were made according to each individual’s clinical response. All 4 of our patients demonstrated sustained clinical response after restarting onabotulinumtoxinA. Further studies are needed to explain why the anamnestic immune response does not return in patients with SD who become secondarily nonresponsive.

Author Contributions

Niv Mor, concept and design of the work; acquisition, analysis, and interpretation of data, drafting the manuscript; revising them manuscript and final approval for publication; Christopher Tang, concept design, acquisition, analysis, and interpretation of data, drafting the manuscript; manuscript revision and final approval for publication; Andrew Blitzer, concept and design of the work; analysis, and interpretation of data; revising the manuscript and final approval for publication.

Disclosures

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References