Focal Dystonia and Botulinum Toxin: Our Experience with IncobotulinumtoxinA

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Abstract

Botulinum toxin type A (BTX-A) represent the gold standard therapy for focal dystonia and related hyperkinetic movement disorders. The main advantages of this method are low rate of complications, reversibility and efficacy in reducing spastic hypertonia or abnormal movements. The treatment is safe but it needs to be repeated periodically and some patients do not obtain effective control of the symptoms due to the onset of secondary immune resistance. For this reason we have selected 45 cases already in treatment with botulinum toxin that have been switched to incobotulinumtoxinA. At a median follow up of 8 months the greatest part of the patients, twenty-six (57.7%) remained clinically unchanged; fourteen (31.1%) had a significant clinical improvement and five (11.1%) worsened. We did not observe any general or injection site complications.

Keywords: Focal dystonia; Botulinum toxin; Hemifacial spasm; Immune response

Introduction

Focal Dystonia (FD) is a hyperkinetic movement disorder which may determine an important functional dysfunctions and significant alteration of the patient's social aspects. This entity is characterized by involuntary prolonged muscular contractions that can cause torsion, repetitive movements, abnormal postures that are often accompanied by pain and tremor [1]. There are many types of dystonia with differing and overlapping pathophysiologic features. FD can be divided from a clinical point of view in generalized, segmental and focal type [2]. Among this last one the most frequent are the Cervical Dystonia (CD), the Blepharospasm (BSP) and the Hemifacial Spasm (HS). Different modalities of treatment have been proposed for these pathologies with the first-line of therapy, by recent guidelines, being the use of botulinum toxin (BoNT) [3]. The toxin was the first time used in the late 1970s in ophthalmology to treat strabismus [4] and over the last 20 years has gained widespread use in conditions requiring inhibition of excessive muscle spasm. This therapy is especially useful for the idiopathic forms [5]. There are two distinct serotypes of BoNT available in clinical practice with various different formulations of serotypes A and B being used. Concerning the type A there are, currently, three leading BoNT: onabotulinumtoxinA (Botox), abobotulinumtoxinA (Dysport) and incobotulinumtoxinA (Xeomin). Among the type B the most used one is the rimabotulinumtoxinB (Myobloc) and this is used only if there is a resistance to type A. After intramuscular injection the beginning of toxin effect can be expected within 3-4 days with a peak in about 2 weeks. This effect is maintained for approximately 8 weeks and then gradually wean off and the injection must be repeated on a regular base. This fact, together with the patient own immunogenicity and the presence within the toxin of immunogenic factors may cause to develop a secondary resistance to ongoing treatment in about 4.3% to 10.5% [6] of subjects following prolonged treatment. Generally most patients may develop treatment failure within 40 months of starting BoNT treatment [7]. Regarding the diffusion profiles of different botulinum toxins A it is possible to find different data in the literature. In a study Carli et al. in 2009 [8] did not find any significant difference between onabotulinumtoxinA, abobotulinumtoxinA and incobotulinumtoxinA while in other studies it was found a greater tendency of abobotulinumtoxinA to produce a significantly greater area of diffusion versus incobotulinumtoxinA at comparable doses and identical volumes of injections [9,10]. The aim of this study was to report and describe changes in clinical scores for focal dystonia after a rapid switch from onabotulinumtoxinA and abobotulinumtoxinA to incobotulinumtoxinA.
Materials and Methods

On a total of 124 patients in treatment with BoNT for dystonia seen in our dedicated outpatient clinic, 45 cases (36.2%) have been selected. All of these had their usual BoNT treatment switched to Xeomin. The patients were prospectively followed up from September 2016 until August 2017 and evaluated by three different scales on the basis of the different types of dystonia: Blepharospasm Disability Index (BDI); Jankovic Rating Scale (JRS) and Toronto Spasmodic Torticollis Rating Scale (TWSTRS). All these patients have already been in treatment with a BoNT: Botox (6 cases) and Dysport (39 cases). Twenty-three patients (51.1%) were affected by CD; twelve (26.6%) by HS and ten (22.2%) by BSP. Twenty-six were women and 19 men with a male to female ratio of 0.7:1. The median age was 71 years with a range between 36 and 98 years old. The median duration of symptoms was from a minimum of 6 years to a maximum of 15 (median 10 years) and all have been on medical treatment with toxin from a minimum of 5 years to a maximum of 14.5 years (Table 1).

The amount of Xeomin toxin used was a mean doses of 35 U for each eye (median 45 units) for the BSP and HS and a mean doses of 200 U in patients with CD. Every patient have had at least 4 treatments with an interval, between consecutive doses, of a minimum of six to eight weeks. Twenty-three (51.1%) received five treatments. The median follow up was 8 months with a range between 6 and 18 months. All patients were injected in the same anatomical points and by the same physician.

Results

The greatest part of the patients, twenty-six (57.7%) remained clinically unchanged compared to the results they used to have with the previously used BoNT (24 Dysport and 2 Botox). Of these 15 were suffering from CD; 5 from HS and 6 from BSP. In addition 14 patients (31.1%) have shown a significant clinical improvement. Among these, 12 were using Dysport respectively for CD (5 cases), HS (6 cases) and BSP (1 case) and two Botox for BSP. Unfortunately we also had 5 patients (11.1%) with a mild clinical worsening; three were suffering from CD and were using Dysport; one from HS and was in treatment with Botox and the last one was treated with Botox for BSP. We did not observe any general or injection site complications (Table 2).

It can affect the neck, face and eye/eyes. CD, also called spasmodic torticollis is the most common form of adult-onset of focal dystonia. It is characterized by involuntary, usually painful, head posturing. The etiology is still not fully understood but it could be the consequence of same type of inhibition of the central nervous system with abnormal sensory-motor integration. HS is an involuntary synchronous tonic and/or clonic contraction of facial muscles, caused by dysfunction of the ipsilateral facial nerve. It can be confused with other movement disorders like benign essential blepharospasm. It has a female predominance with peak onset in the 40-60 year of age. Orbicularis

![](Graph_1.png) Graph 1: JRS Scale for Hemifacial Spasm.

<table>
<thead>
<tr>
<th>N. of Cases</th>
<th>Age</th>
<th>Male</th>
<th>Female</th>
<th>Length of Symptomatology</th>
<th>Hemifacial Spasm</th>
<th>Cervical Dystonia</th>
<th>Blepharospasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>Media 71 yrs</td>
<td>19</td>
<td>26</td>
<td>Median 10 yrs</td>
<td>12</td>
<td>23</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>36-98</td>
<td>42.20%</td>
<td>57.7</td>
<td>6-15 anni</td>
<td>26.60%</td>
<td>51.10%</td>
<td>22.20%</td>
</tr>
</tbody>
</table>

Table 1: Demographic and patients informations.

<table>
<thead>
<tr>
<th>Improved</th>
<th>Unchanged</th>
<th>Worse</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>26</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>31.10%</td>
<td>57.70%</td>
<td>11.10%</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Patients’ result.

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>3</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Graph 2: BDI for Blepharospasm.

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Graph 3: TWSTRS for Cervical Dystonia.

remedy to carry out injection with an interval less than 10-12 weeks. This ineffective it has been formulated two main recommendations:

- The repetitive and spasmodic eye contractions can lead to functional blindness in up to 15% of patients [13]. It is almost exclusively binocular. BSP primarily affects women in their fifties and sixties with a female to male ratio 2-3 to 1 [14]. There are two forms: primary and secondary. Primary disease is the most common encountered in clinical practice probably with a higher incidence in Caucasian race [15]. Secondary disease accounts for less than 10% of all cases and are encountered after focal insults of basal ganglia, cortex, thalamus or brainstem [15]. The standard treatment for these types of primary focal dystonia is the use of BoNT which is a powerful biological toxin produced by Clostridium botulinum. The therapeutic potential of all BoNT serotypes derives from their ability to inhibit the release of acetylcholine from the presynaptic nerve terminal into the synaptic cleft as well the toxin could have also an effect of reducing in sensory input and fewer decrease the muscles contraction [16]. However, the effects of BoNT treatment are temporary which may be attributed to the re-establishment of synaptic contacts with the denervated muscle through a proposed mechanism of motor-neurone sprouting [17]. The duration of the BoNT treatment effect varies from patient to patient and generally may last from 9 to 17 weeks [18]. Some of the patients who receive treatment with TBA may develop a clinical resistance secondary to the formation of antibodies which would decrease the therapeutic effect of the toxin to the point to even neutralize it. This immunogenicity effect would derive from the presence, in the used toxin, of complexing proteins which would stimulate the immunitary system. It seems, exactly that the repeated injections would be the cause of such reaction [19]. Antibodies induced failure of treatment usually develops within the first 2-3 years of BoNT treatment [20,21]. Other reasons for decreased clinical effects may be errors related to drug preparation or administration (storage and reconstitution), improper selection of muscles, inadequate doses per injection site or area or the reagility of the immune system of the individual patients. In order to avoid this possible reduction of the therapeutic efficaciousness it has been formulated two main recommendations: the first is not to overdose the medication and the second is not to carry out injection with an interval less than 10-12 weeks. This problem has driven several pharmaceutical companies to develop toxin free of complexing proteins [22]. It is therefore good practice to administer doses that are sufficient to provide meaningful duration of clinical effect. For all these reasons we have decided to perform this study switching all the patients from the toxin they were using (Botox or Dysport) to a BoNT called Xeomin which should not have any risk or less risk of driving an immunological reaction being composed by a monomeric botulinum neurotoxin of 150 kD, whereas conventional BoNT preparation consist of botulinum neurotoxin-complexing proteins dimers of 600-900 kD. As matter of fact experiment with Xeomin suggest that the absence of complexing proteins is associated with reduced immunogenicity or as it has been shown by Sankahla et al. [23] we can also assist to spontaneous disappearance of BTX-A antibody just after the cessation of the used toxin’s application. We do not know exactly how to interpret the five negative results we had. Perhaps we could have made some mistakes in inadequate dosing, handling errors during drug storage or preparation or even with drug administration (e.g. injection into the wrong muscle). Regarding possible mistakes during the dilution protocol, this eventuality is, in our opinion, very difficult in consideration we have used, like described in various studies, a dose ratio 1:1 for Botox to Xeomin and 3:1 from Dysport to Xeomin [24-26]. Common adverse events associated with BoNT treatment include injection-site pain and diffusion of the toxin from the injection spot to neighbouring muscles causing symptoms such as dysphagia, ptosis, diplopia or limb weakness. However, these complications are generally, transient and mild to moderate in severity. In our study, we did not register any side effect. Regarding the results, a third of the patients improved while half remained unchanged. We have also to remember that all the patients enrolled into the study had been treated with BoNT for a long time and therefore they were at a higher risk of developing immunological resistance. Although there is not any agreement on appropriate assessment using a scales we tried to measure our result using the JRS for the hemifacial spasm; the BDI for the blefarospasm and the TWSTRS for the cervical dystonia. We must say we found them very useful in order to discuss and report different patients result. Another important finding was the fact that the injections intervals became much more flexible and tailored to the patient requirement. They were performed, in same cases as early as 6 weeks after a previous treatment. Dispute this more frequent modality of administration we did not observe any increasing in the adverse events. This was something, really well accepted and loved by the patients. A further advantage, we have encountered in using the Xeomin is its possibility of being kept at room temperature for a ready use and without the necessity of having a cooling system.

Conclusion

The clinical results obtained on this series with the absences of side effects suggest that switching therapy, even if this is done rapidly, from a complexing proteins-containing product to another which has low immunogenicity like Xeomin, may be a viable therapeutic option [27]. Xeomin exhibited consistent and comparable efficacy in the treatment and a safety profiles. We must recognize that potential limitations of this study are the nature of data collection and the reliance on patient-self report outcome to assess efficacy and duration of the treatment but many studies rely on patient-reported information and this is typical of the routine clinical practice. On the other hand, one strength of the study, is that all the patient have been treated by just one experienced physician making, in this way, the technique for the different types of dystonia much more uniform. Certainly a double blind randomized study would be very useful to draw more firm conclusion. However, switching from abobotulinumtoxinA and onabotulinumtoxinA to incobotulinumtoxinA with respectively a 3:1 to 1:3 ratio conclusion. However, switching from abobotulinumtoxinA to incobotulinumtoxinA with respectively a 3:1 ratio from onabotulinumtoxinA to incobotulinumtoxinA with respectively a 3:1 ratio from onabotulinumtoxinA to incobotulinumtoxinA with respectively a 3:1 ratio from onabotulinumtoxinA to incobotulinumtoxinA with respectively a 3:1 ratio from onabotulinumtoxinA to incobotulinumtoxinA with respectively a 3:1 ratio from onabotulinumtoxinA to incobotulinumtoxinA with respectively a 3:1
and 1:1 units ratio resulted in good therapeutic effectiveness in terms of treatment efficacy, duration effects and adverse events.

References


