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.

Key Words: focal dystonia, botulinum toxin, hemifacial spasm, immune response

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Introduction

Focal dystonia (FD) is a hyperkinetic movement disorder which may determine an important functional dysfunctions and significant alteration of the patients 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 [Albanese *et al*., 2013]. There are many types of dystonia with different and overlapping pathophysiologic features. FD can be divided from a clinical point of view in generalized, segmental and focal type (Jankovic *et al*., 2007). 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) (Albanese *et al*., 2011). The toxin was the first time used in the late 1970s in ophthalmology to treat strabismus (Scott AB, 1980) 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 (Costa *et al*., 2004). 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: anabotulinumtoxinA (Botox), abobotulinumtoxinA (Dysport) and incobotulinumtoxinA (Xeomin). Among the type B the most used one is the rimabotulinumtoxin B (Myobloc) which 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 weans off and the injection must be repeated on a

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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 4.3-10.5% (Kessler and Benecke, 1997) of subjects following prolonged treatment. Generally most patients may develop treatment failure within 40 months of starting BoNT treatment (Dressler, 2002). 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 did not find any significant difference between anabotulinumtoxinA, 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 (Ranoux *et al*., 2002; Kerscher *et al*., 2007). The aim of this study was to report and describe changes in clinical scores for focal dystonia after a rapid switch from anabotulinumtoxinA and abobotulinumtoxinA to incobotulinumtoxin A.

Materials and Methods

On a total of 124 patients in treatment with BoNT for dystonia seen in our dedicated outpatient clinic, 45 random 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: Blepharospsasm 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 minumum 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 patients 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 site.

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).

Among the 14 who got better the Jankovic Rating Scale for HS went down from a median of 6 to 2.5 (graph 1);

Blepharospasm Disability Index for the BSP went from a median of 3.5 to 2 (graph 2);

while the Toronto Spasmodic Torticollis Rating Scale for the CD changed from a median of 65 to 30 (graph 3).

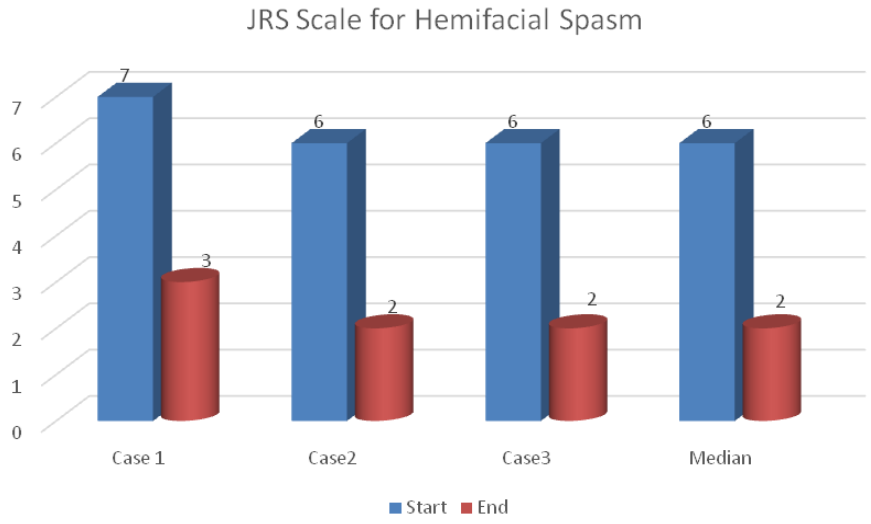
In the same time the injection intervals became more flexible from a minimum of 6 to a maximum of 17 weeks.

Discussion

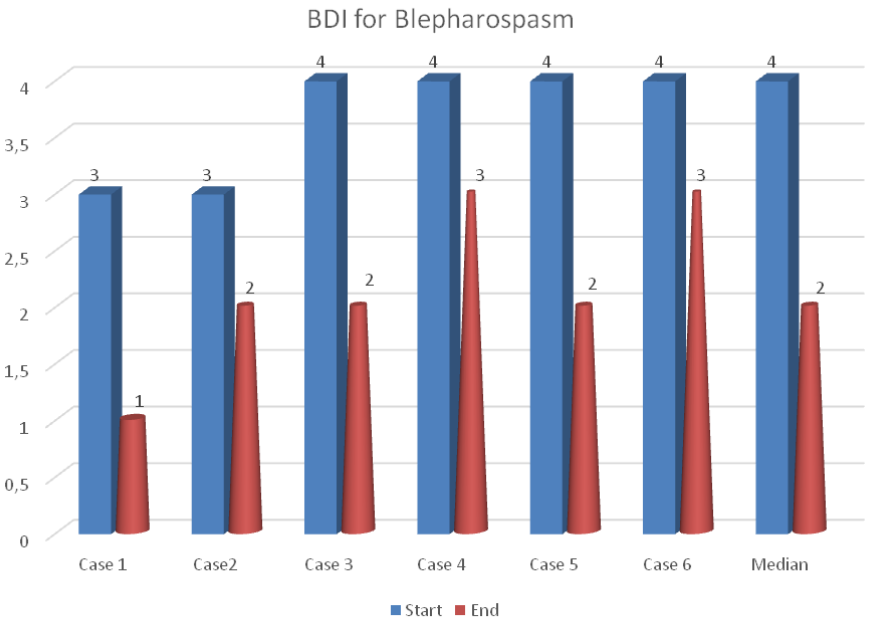
Dystonia is the third most common movement disorders after Parkinson disease and essential tremor which has an overall prevalence of 164 per million (Steeves *et al*., 2012). The patient with dystonia has painful involuntary sustained or

Table 1. Demographic and patients informations.

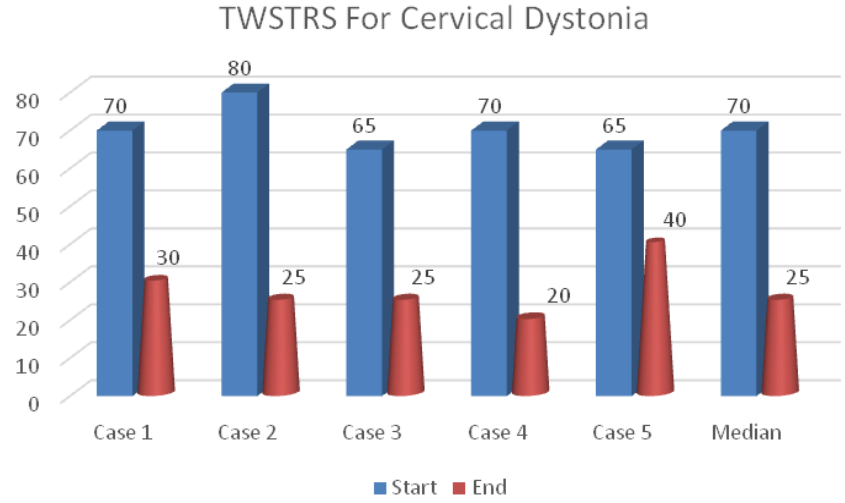
N. OF CASES	AGE	MALE	FEMALE	LENGTH OF SYNTOMATOLOGY	HEMIFACIAL SPASM	CERVICAL DYSTONIA	BLEPHAROSPASM
45	**Media 71 yrs** 36-98	**19** 42.2%	**26** 57.7	**Median 10 yrs** 6-15 anni	**12** 26.6%	**23** 51.1%	**10** 22.2%



Graph 1



Graph 2



Graph 3

Table 2. Patients' result.

IMPROVED	UNCHANGED	WORSE	COMPLICATIONS
14 31.1% **BLEPHAROSPASM** 3 **CERVICAL DYSTONIA** 5 **EMIFACIAL SPASM** 6	**26** 57.7% **BLEPHAROSPASM** 6 **CERVICAL DYSTONIA** 15 **EMIFACIAL SPASM** 5	**5** 11.1% **BLEPHAROSPASM** 1 **CERVICALDYSTONIA** 3 **EMIPHACIAL SPASM** 1	**0**

intermittent muscles contraction causing abnormal and often repetitive movements or posture of the face, neck, limbs or trunks. Focal dystonia is a highly disabling movement disorder with serious social and functional impairment. 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 a peak onset in the 40-60 year of age. Orbicularis oculi is the initial site of spasm in 90% of patients. The third type of focal dystonia, the benign essential BSP, also called idiopathic blepharospasm is considered an adult onset of dystonia. It is characterized by involuntary lid closure by spontaneous, spasmodic, bilateral, intermittent or persistent involuntary contractions of the orbicular oculi muscles and other periorbital muscles (Vitek JL, 2002). The repetitive and spasmodic eye contractions can lead to functional blindness in up of 15% of patients (Roggenkamper *et al*., 2006). It is almost exclusively binocular. BSP primarily affects women in their fifties and sixties with a female to male ratio 2-3 to 1 (Anderson *et al*., 1998). 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 (Green *et al*., 2017). Secondary disease accounts for less than 10% of all cases and are encountered after focal insults of basal ganglia, cortex, thalamus or brainstem (Green *et al*., 2017). 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 (Matak and Lack0wic, 2014). 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 (De Paiva *et al*., 1999). The duration of the BoNT treatment effect varies from patient to patient and generally may last from 9 to 17 weeks (Marsh *et al*., 2014). 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 (Dressler D, 2004). Antibodies induced failure of treatment usually develops within the first 2-3 years of BoNT treatment (Dressler *et al*., 2003; Newmann *et al*., 2010). 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 reagibility 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 (Jost *et al*., 2007). 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*. (1998) 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 such inadequate dosing, handling errors during drug storage or preparation or even with drug administration (eg. injection into the wrong muscle). Regarding possible mistakes during the 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 (Prager *et al*., 2011; Sanpaio *et al*., 1997; Odergreen *et al*., 1998). 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.

Conclusions

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 (Santamato *et al*., 2012). 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 assesss 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 and 1:1 units ratio resulted in good therapeutic effectiveness in terms of treatment efficacy, duration effects and adverse events.

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References

Albanese A, Bathia K, Bressman SB, Delong MR, Fahn S. Phenomenology and classification of dystonia: a consensus update. Movement disorders 2013; 28(7): 863-873.

Albanese A, Asmus F, Bhatia KP, Elia AE, Elibol B, Filippini G, Gasser T, Krauss JK, Nardocci N, Newton A., Valls-Sole J. EFNS guidelines on diagnosis and treatment of primary dystonias. European Journal Neurology 2011; 18: 5-18.

Anderson RL, Patel BC, Holds JB, Jordan DR, Blepharospam: past

present and future. Ophthalmology Plastic Reconstructive Surgery 1998; 14: 305-317

Carli L, Montecucco C, Rossetto O. Assay of diffusion of different botulinum neurotoxin type a formulations injected in the mouse leg. Muscle & Nerve: Official Journal of the American Association of Electrodiagnostic Medicine. 2009; 40(3): 374-80.

Costa J, Espírito-Santo CC, Borges AA, Ferreira J, Coelho MM, Moore P, Sampaio C. Botulinum toxin type A therapy for blepharospasm. Cochrane Database of Systematic Reviews. 2004; 2.

De Paiva A, Meunier FA, Molgo J, Aoki KR, Dolly JO. Functional repair of motor endplates after botulinum neurotoxin type A poisoning: biphasic switch of synaptic activity between nerve sprouts and their parent terminals. Procedure National Academic Sciences, USA 1999; 96: 3200-3205.

Dressler D, Clinical presentation and management of antibody-induced failure of botulinum toxin therapy. Movement Disorders 2004; 19: S92-S100.

Dressler D, Benecke R, Bigalke H. Botulinum toxin type B (neurobloc) in patients with botulinum toxin tuype A antibody-induced therapy failure. Journal of Neurolology 2017; 250: 967-969.

Dressler D. Clinical features of antibody-induced complete secondary failure of botulinum toxin therapy. European Neurology 2002; 48: 26-29.

Green KE, Rastall D, Eggenberger E. Treatmnt of blepharospasm/ hemifacial spasm. Current Treatment Options Neurology 2017; 19: 41.

Jankovic J, Tsui J, Bergeron C. Prevalence of cervical dystonia and spasmodic torticollis in the United States general population. Parkinsonism & Related Disorders 2007; 13(7): 411-416.

Jost WH, Brumel J, Grafe S. Botulinum neurotoxin type A free of complexing proteins (Xeomin) in focal Dystonia. Drugs 2007; 67: 669-683.

Kerscher M, Maack M, Reuther T, Kruger N. Diffusion characteristics of two different neurotoxins in patients with symmetric forehead lines. Journal American Academy Dermatology 2007; 56: AB199.

Kessler KR and Benecke R. The EBD test - a clinical test for the detection of antibodies to botulinum toxin type A. Movements Disorders 1997; 12: 95-99.

Marsh WA, Monroe DM, Brin MF, Gallagher CJ. Systematic review and meta-analysis of the duration of clinical effect of onabotulinumtoxinA in cervical dystonia. BMC Neurology 2014; 14: 91.

Matak I and Lackowic Z. Botulinum toxin type A: brain and pain. Progress in Neurobiology 2014; 119-120: 39-59.

Naumann M, Carruthers A, Carruthers J. Meta Analysis of neutralizing antibody conversion with onabotulinumtoxin (Botox) across multiple indications. Movement Disorders 2010; 25: 2211-2218.

Odergren T, Hjaltason H, Kaakkola S, Solders G, Hanko J, Fehling C. A double blind, randomised, parallel group study to investigate the dose equivalence of Dysport and Botox in the treatment of cevical dystonia. Journal Neurology Neurosurgery and Psychiatyry 1998; 64: 6-12.

Prager W, Prager W, Wissmuller E, Kollhorst B, Boer A, Zschocke L. Treatment of crow's feet with two different botulinum toxin type A preparations in split-face technique. Hautarzt 2011; 62: 375-379.

Ranoux D, Gury C, Fondarai J, Mas JL, Zuber M. Respective potencies of Botox and Dysport: a double blind, randomised, crossover study in cervical dystonia. Journal Neurology Neurosurgery and psicgiatry 2002; 72: 459-462.

Roggenkamper P, Jost WH, Bihari K, Comes G, Grafe S. Efficacy and safety of a new botulinum toxin type A free of complexing proteins in the treatment of blepharospsasm. Journal of Neural Trasmission 2006; 113: 303-312.

Sankhala C, Jankovic J, Duane D. Variability of the immunologic and clinical response in dystonic patients immunoresistant to botulinum toxin injections. Movement Disorders 1998; 13: 150-154.

Sanpaio C, Ferreira JJ, Simoes F, Rosas MJ, Magalhaes M, Correia AP. DYSPOT: a single-blind, randomized parallel study to determine whether any differences can be detected in the effcicacy and tolerability of two formulations of botulinum toxin type A-Dysport and Botox- assuming a ratio of 4:1. Movement Disorders 1997;12: 1013-1018.

Santamato A, Ranieri M, Panza F, Frisardi V, Micello MF, Filoni S. Effectiveness of switching therapy from complexing protein containing botulinum toxin type A to a formulation with low immunogenicity in spasticity after stroke: a case report. Journal Rehabilitation Medicine 2012; 44: 795-797.

Scott AB. Botulinum toxin injection into extraocular muscles as an alternative to strabismus surgery. Journal Pediatric Ophtalmology Strabismus 1980; 17: 21-25.

Steeves TD, Day L, Dykeman J, Jette N, Pringsheim T. The prevalence of primary distonia: a systematic review and meta-analysis. Movement Disorders 2012; 27(14): 1789-1796.

Vitek JL. Pathophysiology of dystonia: a neuronal model. Movement Disorders 2002; 17: S49-S62.