Movement Disorders
CLINICAL PRACTICE

CASE REPORT

Clinical Response to IncobotulinumtoxinA, after Demonstrated Loss of Clinical Response to OnabotulinumtoxinA and RimabotulininumtoxinB in a Patient with Musician's Dystonia

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Botulinum toxin is a mainstay therapy for dystonia. Formulations available are three types of botulinumtoxinA and one type of botulinumtoxinB.[1] Antibodies can develop against the toxin, leading to treatment failure. IncobotulinumtoxinA (Xeomin; Merz Pharmaceuticals GmbH, Frankfurt, Germany) is differentiated from other types of botulinumtoxinA preparations by being free from complexing proteins, speculated to make the product less antigenic.[2]

Methods

We report on a patient with musician's cramp with good therapeutic response to incobotulinumtoxinA after there was a loss of clinical benefit in the patient and a negative frontalis test with onabotulinumtoxinA (BOTOX; Allergan, Inc., Irvine, CA) and rimabotulinumtoxinB (Myobloc/Neurobloc; Solstice Neurosciences, San Francisco, CA). Though there were different injectors, the supervising attendings were consistent and electromyography (EMG) and ultrasound (US) were utilized.

Results

A 65-year-old man had musician's cramp since age 30, with left-hand fourth finger metacarpophalangeal joint flexion and interphalangeal joint extension on pressing violin strings (see Video). His treatment course is described in Table 1. He received onabotulinumtoxinA, mostly into the second and third lumbricals. He initially reported fair benefit (20%–50%), using a self-reported visual analog scale ranging from 0% (no improvement) to 100% (normal use). Some variability between treatment cycles was noted in magnitude and duration of responses, including postinjection weakness. The injection interval was determined by the patient's symptoms, as well as need for high-level performance. Between the sixth to mid-seventh years of treatment, the benefit reached 50% to 60%. He then skipped injections for 6 months because he was doing well. After resuming at the previously effective dose of onabotulinumtoxinA, there was 0% benefit and no weakness, despite injection at a higher dose. Frontalis testing with a single 15-unit dose injection showed resistance to onabotulinumtoxinA. He was switched to rimabotulinumtoxinB from the eighth to the mid-ninth year of treatment, with 10% to 35% benefit. Late in the ninth year of treatment, he reported 0% benefit and no weakness with doses up to 1,500 units. Frontalis testing with a 500-unit dose injection of rimabotulinumtoxinB showed resistance. Frontalis testing with a 15-unit dose injection of incobotulinumtoxinA showed a positive response (Fig. 1). He was switched to incobotulinumtoxinA and has had 50% to 60% benefit in four cycles over 1.5 years and has been able to continue playing as a professional violinist.

Discussion

Musician's cramp is a task-specific dystonia, with patients typically unable to continue careers as professional musicians.[3] Botulinum toxin injection is safe and effective in the long-term treatment of patients with focal hand dystonia.[2] Response to subsequent botulinum toxin injections is reliably predicted by the frontalis test,[4] which guided the decision to switch botulinum toxin formulations twice in this case. The frontalis test is a sensitive biological test for immunoresistance, correlating well with the presence of neutralizing antibodies detected by the in vivo mouse protection bioassay and western blotting assay.[4]

IncobotulinumtoxinA has not been associated with development of neutralizing antibodies, possibly because of the absence of complexing proteins.[5,6] A patient with poststroke spasticity responded well to incobotulinumtoxinA, after being a secondary nonresponder to onabotulinumtoxinA, as evidenced by the

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TABLE 1 Treatment course with botulinum toxin over 10 yr

Date of Treatment	Toxin Type	Dose (Units)	% Weakness	% Benefit
August 2001	Ona	45	0	50
December 2001		50	50	20
February 2002		65	30	20
June 2002		50	20	50
August 2002		45	20	50
December 2002		35	25	50
July 2003		40		
April 2004		30	60	20
December 2004		20	50	40
January 2006		15	10	10
July 2006		20	40	60
August 2007		15	35	55
December 2007		17.5	20	50
June 2008		22.5	0	0
December 2008		30	0	0
		15 units Frontalis test	Negative	
January 2009	Rima	900	10	20
March 2009		1000	70	25
September 2009		1000	25	25
December 2009		600	15	10
March 2010		700	10	10
September 2010		800	10	35
November 2010		1000	0	0
January 2011		500 units Frontalis test 1500	Negative	
February 2011	Inco	15 units Frontalis test 17	Positive	
May 2011		20	25	55
December 2011		20	50	60
July 2012		17.5	10	60
January 2013		16	25	50

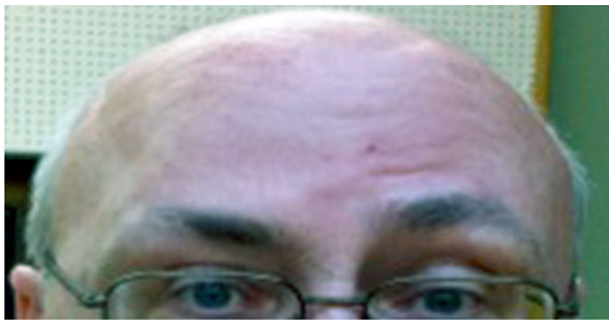

Figure 1 Positive frontalis test. Asymmetric brow raising resulting from weakness of the right frontalis muscle after injection with incobotulinumtoxinA.

extensor digitorum brevis test.[7] Neither this patient nor our patient had laboratory testing for antibodies; but, in both cases, resistance was demonstrated by frontalis testing, which is more clinically valuable. Whereas the development of antibodies may be associated with the complexing proteins, the neutralizing antibodies detected by lab assays are reported to be against the toxin serotype (A or B), rather than the complexing proteins. In such a case, however, it would seem unlikely that incobotulinumtoxinA would restore response.

The long interval between the last onabotulinumtoxinA and the initiation of incobotulinumtoxinA might be relevant. We acknowledge the potential for a decline in resistance with time and/or the risk of redevelopment of immunoresistance, and that it is not known whether the patient would have responded again to onabotulinumtoxinA or rimabotulinumtoxinB. When there is immunoresistance to onabotulinumtoxinA, after a long interval, the person may respond again for at least one cycle, but then often quickly redevelops immunoresistance.[8] Antibody level may drop and then return. However, if incobotulinumtoxinA is less antigenic, in this situation, the antibodies might not return. Our patient demonstrated steady and continued response to incobotulinumtoxinA for more than 1.5 years.

We no longer test for antibodies in our patients showing signs of nonresponse and go directly to frontalis testing. This is because we are interested in clinical responsivity, which the frontalis test directly measures. Patients can become nonresponders even without demonstration of antibodies.

Factors other than neutralizing antibodies can explain treatment failure, such as errors related to toxin preparation, storage or reconstitution, muscle selection, inadequate dosing per injection site, or changes in disease presentation or expectations,[7] and injection skill. In this case, however, these factors have been stable and maximal doses have been tried, with US and EMG guidance for adequate muscle localization.

It could be that our patient simply had a fluctuating response, which is not uncommon in musician's dystonia,[3] but such patients are usually unable to continue performing. This is important to consider, especially given that the patient's incobotulinumtoxinA dose is significantly less than commonly used equivalent dosing with his previous onabotulinumtoxinA. Recent meta-analyses show no difference in potencies between onabotulinumtoxinA and incoboutlinumtoxinA.[9] More studies are necessary to determine clinically relevant differences in biological activity and potency of the different toxin types.[10] EMG showing lack of denervation to confirm the case as a true resistance would have been useful.

In conclusion, this case report suggests that switching to other types of botulinum toxin should be studied further in larger studies given that such a strategy might be considered as a viable treatment option.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

V.F.M.L.R.: 1A, 1B, 1C, 2B, 2C, 3A, 3B

B.I.K: 1A, 1B, 1C, 2B, 2C, 3B

C.L: 1A, 1B, 1C, 2B, 2C, 3B

K.A.: 1A, 1B, 1C, 2B, 2C, 3B

M.H.: 1A, 1B, 1C, 2B, 2C, 3B

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Supporting Information

A video accompanying this article is available in the supporting information here.

Video. Musician's dystonia in the left hand, with fourth finger metacarpophalangeal joint flexion and third interphalangeal joint extension on pressing violin strings.

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