Botulinum Toxin Type B Observational Study (BOS)

Jankovic J, Hunter C, Atassi MZ, Dolimbek BZ, Dolimbek GS, and BOS Research Group

Baylor College of Medicine, Houston, Texas

Abstract

OBJECTIVE: To examine safety and efficacy of botulinum toxin type B (BTX-B) in patients with cervical dystonia (CD) and to correlate the response with the presence of blocking antibodies (Abs). **BACKGROUND:** Although the frequency of blocking Abs has decreased since the shift in 1998 to a new formulation of BTX-A (BOTOX®, Allergan), the possibility of immunoresistance must be considered in patients with secondary unresponsiveness (Jankovic et al. Neurology 2003;60:1186). Development of secondary unresponsiveness to BTX-A usually improves with BTX-B, an antigenically distinct neurotoxin. Some patients, however, become unresponsive to BTX-B after repeated injections, presumably due to development of blocking Abs (Berman et al. Mov Disord 2005;20:233). While there are several methods used to detect and measure BTX-A Abs, no validated method for detecting BTX-B Abs is available. **METHODS:** BOS is a 10-center, observational study of CD patients treated with BTX-B. The study has three components: 1) Retrospective data of prior exposure to BTX-B; 2) Prospective data of current treatment with BTX-B; and 3) Immunological status (presence or absence of blocking Abs) before and after exposure to BTX-B. Each visit included patient assessment of response to prior treatment, onset/duration of response, functional ability, and pain, physician assessment of severity, tremor, Toronto Western Spasmodic Torticollis Rating Scale, injection information (dose, muscles), and adverse events (AEs). **RESULTS:** Total of 120 patients were enrolled with prospective data available on 105 (85 female). Abs status is currently available on (430/474) 91% of total samples collected. At baseline, 15 (13%) of patients exposed to BTX-B had evidence of blocking Abs, whereas 11 (9%) of those exposed to BTX-A (73% treated with the original BTX-A) had blocking Abs as measured by the mouse protection assay ($p<0.003$). The most frequent AEs attributed to BTX-B included dry mouth 17 (14%), dysphagia 14 (12%), GI symptoms 5 (4%), severe pain at injection site 4 (3%), and blurred vision 2 (1.6%). Twenty-six (22%) withdrew due to lack of efficacy of □ BTX-B, 25 (21%) have returned to treatment with BTX-A, 20 (17%) other treatment, 7 (5.9%) surgical treatment, and 8 (6.7%) are lost to follow-up. **CONCLUSION:** BTX-B offers a useful alternative to patients with immunoresistance to BTX-A, but long-term efficacy is limited by the development of blocking Abs, probably as a result of cross-reactivity between the two serotypes.

Introduction

Since its introduction of botulinum toxin (BTX) into clinical use in the early 1980s, BTX has been demonstrated to provide an effective and safe therapy for focal and segmental dystonia as well as other disorders manifested by inappropriate contractions of muscles. Approved by the Food and Drug Administration (FDA) in 1989 for the treatment of blepharospasm and hemifacial spasm, BTX-A has since become a powerful therapeutic tool in a variety of neurologic and other disorders. In 2000, both BTX-A and BTX-B were approved for the treatment of CD. Although the number of disorders in which BTX has been found to be effective is rapidly expanding, CD continues to be one of the most frequent therapeutic indications. Up to 18% of patients treated chronically for CD with the original (used prior to 1998) BTX-A (BOTOX®, Allergan) and BTX-B (MYOBLOC™, Elan Pharmaceuticals, Inc) develop immunoresistance, manifested by absence of clinical response that correlates with the presence of blocking antibodies (Abs). Although the risk of immunoresistance with the current BTX-A (BOTOX®, Allergan) is markedly lower than with the original preparation (Jankovic et al. Neurology 2003;60:1186) and patients who develop secondary unresponsiveness to BTX-A usually improve with BTX-B, an antigenically distinct neurotoxin, there is a concern about the long-term effects of BTX-B. Preliminary data suggest that some patients become unresponsive to BTX-B after repeated injections , presumably due to development of blocking Abs (Berman et al. Mov Disord 2005;20:233). While there are several methods used to detect and measure BTX-A Abs, no BTX-B Abs assay is currently available. The BOS study was primarily designed to examine the immunogenicity of BTX-B as well as to assess its long-term efficacy and safety.

Table 1. BTX-B Observational Study: Demographics

□ □	n□	Mean□	SD□	Min□	Max
Age (yr)□	119□	59.9□	12.8□	18.7□	85.3
Duration of CD (yr)□	119□	13.7□	8.9□	1.5□	50
Number of Treatment Visits□	106□	5.2□	3.3□	1□	12
Prior Original & Current BTX-A Dose (U)□	73□	4528.0□	2796.4□	90□	15150
Prior Current BTX-A Dose (U)□	22□	1669.9□	1307.0□	175□	5200
Prior BTX-B Dose (U)□	51□	77697.2□	82915.7□	206□	335000

Table 2. Immunological Status at Last Visit

□ □ □ □	BTX-B Ab+□ (N = 34)□		BTX-B Ab- (N = 65)		
Variable□	Mean□	SD□	Mean□	SD□	P
Duration of Treatment (mo)□	12.4□	11.8□	21.1□	10.0□	NS
Duration of CD (yr)□	10.7□	5.6□	15.2□	10.4□	0.006
Number of Visits□	7.0□	2.9□	4.3□	3.2□	0.0001
Total Dose (U)□	97184.4□	51790.8□	56147.1□	55009.3□	0.001

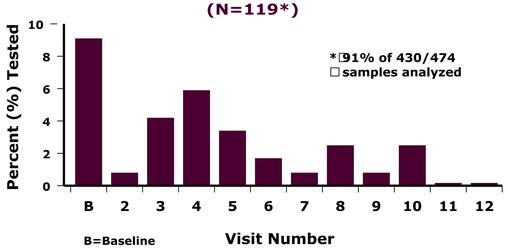
Methods / Results

After signing an informed consent, the patients underwent an evaluation of their CD, TWSTRS rating scale, a physician assessment, and self- assessment. The study-specific, demographic and clinical data, including data about prior treatment and response to BTX-A, rating scale scores, latency from injection to onset of clinical response, peak effect, duration of benefit, AEs, number of muscles injected, dosages were entered into a database. After the baseline visit at which time response to previous BTX-A or BTX-B injection were collected retrospectively and prospectively. At the time of follow up, patients who at any treatment visit were clinically considered "unresponsive" (peak effect score of 1 or 0 in at least one treatment visit) to the previous injection, were be injected with 1,500 units of BTX-B into the right medial eyebrow (unilateral brow injection or UBI) to assess their response to BTX-B (Hanna and Jankovic, 1998).

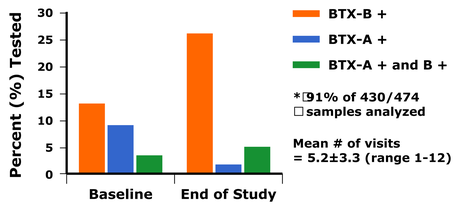
Mouse Protection Assay (MPA)

We used the MPA to determine the presence in the sera of CD patients of blocking Abs against BTX-A or BTX-B. We first determined the survival of outbred (ICR) mice against intravenous injection in the tail of various doses of BTX-A or BTX-B, using 5 mice per dose of each toxin. The BTX-A dose at which no mice survived (i.e., LD100) was 6.2 pg/mouse. For BTX-B, the LD100 was 7.89 pg/mouse. To determine the protective activity of sera from CD patients against BTX-A or BTX-B, ICR mice were injected intravenously in the tail with a mixture of 100 ul of the CD serum and 1.05 x LD100 of active BTX-A or □ BTX-B (i.e., 6.5 pg of BTX-A or 8.29 pg of BTX-B per mouse). Each serum was assayed for blocking Abs against BoNT/A using □ 5 mice and a similar number of mice were used to assay for blocking Abs against BTX-B. The mice were observed 3 times a day for 6 days. In the case that the serum contained blocking Abs, the mice recovered and survived the challenge. When protective Abs were either absent or their amounts too low, then none or only 1 of the mice survived the challenge. If 2-3 out of five mice survived the challenge, then the assay was repeated to obtain a more conclusive result.

Prospective BTX-B Observational Study: BTX-B Antibody Status: New Occurrences (N=119*)



Prospective BTX-B Observational Study: Antibody Status (N=119*)



Mean # of visits = 5.2±3.3 (range 1-12)

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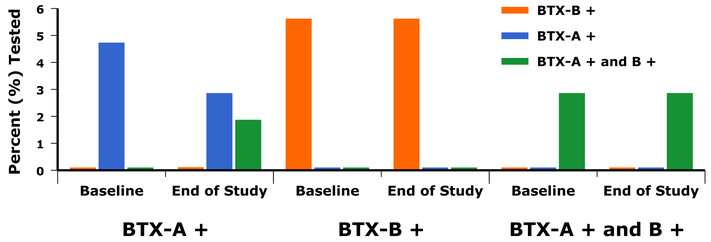
Conclusions

This first study designed to assess the rate of immunoresistance to BTX-B shows that BTX-B offers a useful alternative to patients with immunoresistance to BTX-A, but long-term efficacy is limited by the development of blocking Abs, probably as a result of cross-reactivity between the two serotypes.

Prospective BTX-B Observational Study: Baseline vs End of Study Antibody Status (N=119*)



*91% of 430/474 samples analyzed

BTX-B Observational Study Antibody Status: Cumulative (N=119*, 14 Retrospective Only and 105 Prospective)