

CASE REPORT

IncobotulinumtoxinA for Post-stroke Upper Limb Spasticity in Neutralizing Antibody-positive Patients after Botulinum Toxin Therapy: A Report of Two Cases

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Background: Botulinum toxin type A is an effective treatment widely used to address post-stroke spasticity. Long-term repeated treatment with botulinum toxin type A may result in reduced efficacy due to the induction of neutralizing antibodies. Based on data from a phase 3 study of incobotulinumtoxinA for post-stroke upper limb spasticity, we describe the therapeutic response to botulinum toxin type A treatment in two neutralizing antibody-positive patients previously treated with other preparations of botulinum toxin type A. **Case:** Two patients (a 65-year-old woman and a 36-year-old woman) with post-stroke upper limb spasticity were previously treated with onabotulinumtoxinA, and neutralizing antibodies were detected in their sera at baseline using the mouse hemidiaphragm assay. After onabotulinumtoxinA had been discontinued for at least 16 weeks, incobotulinumtoxinA (400 U) was administered in three or four injection cycles. Good therapeutic responses, manifested by a reduction of 1–2 points on the modified Ashworth scale, were noted after each injection. The patients' sera remained positive for neutralizing antibodies throughout the incobotulinumtoxinA treatment period. **Discussion:** These patients, who were previously treated with onabotulinumtoxinA and were neutralizing antibody positive throughout the clinical study period, showed stable therapeutic responses following incobotulinumtoxinA treatment. IncobotulinumtoxinA could be initiated for patients with neutralizing antibodies induced by onabotulinumtoxinA.

Key Words: botulinum toxins; neurotoxins; stroke; muscle spasticity

INTRODUCTION

Intramuscular injection of botulinum toxin type A (BoNT/A) is an effective and widely used pharmacotherapy for post-stroke limb spasticity. In some patients who receive repeated injections of BoNT/A, a loss of efficacy response, i.e., secondary treatment failure, hinders treatment continuation. The appearance of secondary treatment failure is thought to be caused by various factors, one of which might be

the production of neutralizing antibodies against BoNT/A.¹⁾ The prevalence of neutralizing antibodies in patients with spasticity reaches as high as 15%.^{2–4)} IncobotulinumtoxinA (incoBoNT/A, XEOMIN[®]) consists of only the core botulinum neurotoxin without the complexing proteins that might act as antigens; consequently, incoBoNT/A has low immunogenicity.^{2,3,5)} Herein, two cases were selected from among the participants of a phase 3 study of incoBoNT/A for post-stroke upper limb spasticity.^{6,7)} These patients, who were

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previously treated with onabotulinumtoxinA (onaBoNT/A, BOTOX®) and had neutralizing antibodies throughout the study, showed stable efficacy following incoBoNT/A treatment.

CASES

A multicenter phase 3 study of incoBoNT/A in patients with post-stroke spasticity of the upper limbs was conducted in Japan between November 2015 and April 2018 (J-PURE; JapicCTI -153029, registration date: October 1, 2015, <https://www.clinicaltrials.jp/cti-user/trial/ShowDirect.jsp?clinicalTrialId=30245>). This study included three periods: a lead-in tolerability period (single injection cycle of incoBoNT/A in 11 patients); a 12-week, double-blind, randomized-controlled, main period (MP, single cycle of four arms, i.e., 400 or 250 U of incoBoNT/A, or matching placebo, in 100 patients); and an open-label extension period (OLEX; up to 32–40 weeks, three cycles of incoBoNT/A in 100 patients). This study was conducted in accordance with the ethical principles of the Good Clinical Practice guidelines and the Declaration of Helsinki and was approved by the institutional review boards (approved protocol code: MRZ60201_3099_1). Informed consent was obtained from all individual participants included in the study. Details of the method and results of the study have been reported elsewhere.⁶⁾

In patients who were being treated with onaBoNT/A, treatment was halted regardless of the treatment response or antibody status. These patients spent at least 16 weeks in a washout period before participating in this study. For assessment of immunogenicity, all participants were screened for anti-BoNT/A antibodies using a fluorescence immunoassay; if the result was positive, neutralizing antibodies against incoBoNT/A were determined using the highly specific mouse hemidiaphragm assay (HDA). HDA measures the time to paresis caused by BoNT/A with and without patient serum; if the time is longer with patient serum, the presence of neutralizing antibody is confirmed.⁸⁾ Based on the HDA results (with ≥ 65 min considered positive), three patients tested positive for neutralizing antibodies at study enrollment; of these, two were positive at the end of study, and one was negative after incoBoNT/A administration. Neither secondary non-response nor newly developed neutralizing antibodies were observed during this phase 3 study.⁶⁾ The efficacy of incoBoNT/A was evaluated using the modified Ashworth scale (MAS) for wrist flexors; MAS is a 6-point scale ranging from 0 (no increase in muscle tone) to 4 (af-

ected part[s] rigid in flexion or extension).⁹⁾

CASE A

A 65-year-old woman suffered an ischemic stroke in August 2010 that resulted in left upper limb spasticity. From September 2014 to April 2016, 200–300 U of onaBoNT/A was administered. In August 2016, 18 weeks after the last onaBoNT/A administration, the patient was enrolled in the study. Therein, the patient was assigned to the incoBoNT/A 400 U group for the MP. From September 2016, incoBoNT/A (400 U) was administered in a total of four cycles during the MP and OLEX; the study was completed in July 2017. The dose of incoBoNT/A injected into each muscle⁶⁾ was distributed as follows: 0–50 U for the flexor digitorum profundus, 50–100 U for the flexor digitorum superficialis, 100 U for the biceps, 0–50 U for the brachialis, 0–50 U for the pronator teres, 50–100 U for the flexor carpi radialis, 50 MU for the flexor carpi ulnaris, and 0–50 MU for the flexor pollicis longus.

After the initiation of incoBoNT/A treatment, the MAS score from baseline to week 1 during the MP and to week 4 in each cycle of the OLEX decreased from 3 to 1 and 3 to 1+ or 2, respectively (**Fig. 1A**). The HDA was 140.1 min before the initiation of incoBoNT/A, at the start of the OLEX, and at study completion. No adverse events related to incoBoNT/A injections were observed.

CASE B

A 36-year-old woman suffered a hemorrhagic stroke in December 2007 that resulted in right upper limb spasticity. From December 2014 to May 2016, 350 U of onaBoNT/A was administered. In September 2016, 16 weeks after the last onaBoNT/A administration, the patient was enrolled in the present phase 3 study. In the study, the patient was assigned to the placebo group for the MP. From December 2016, incoBoNT/A (400 U) was administered for three cycles during the OLEX, and the study was completed in August 2017. The dose of incoBoNT/A injected into each muscle⁶⁾ was as follows: 50–60 U for the flexor digitorum profundus, 50–60 U for the flexor digitorum superficialis, 60–70 U for the biceps, 60 U for the pronator teres, 50–60 U for the flexor carpi radialis, 50–60 MU for the flexor carpi ulnaris, and 40–50 U for the flexor pollicis longus.

After the initiation of incoBoNT/A treatment, the MAS score from baseline to week 4 decreased from 3 to 1+ in each cycle (**Fig. 1B**). The HDA was 140.1 min before the initia-

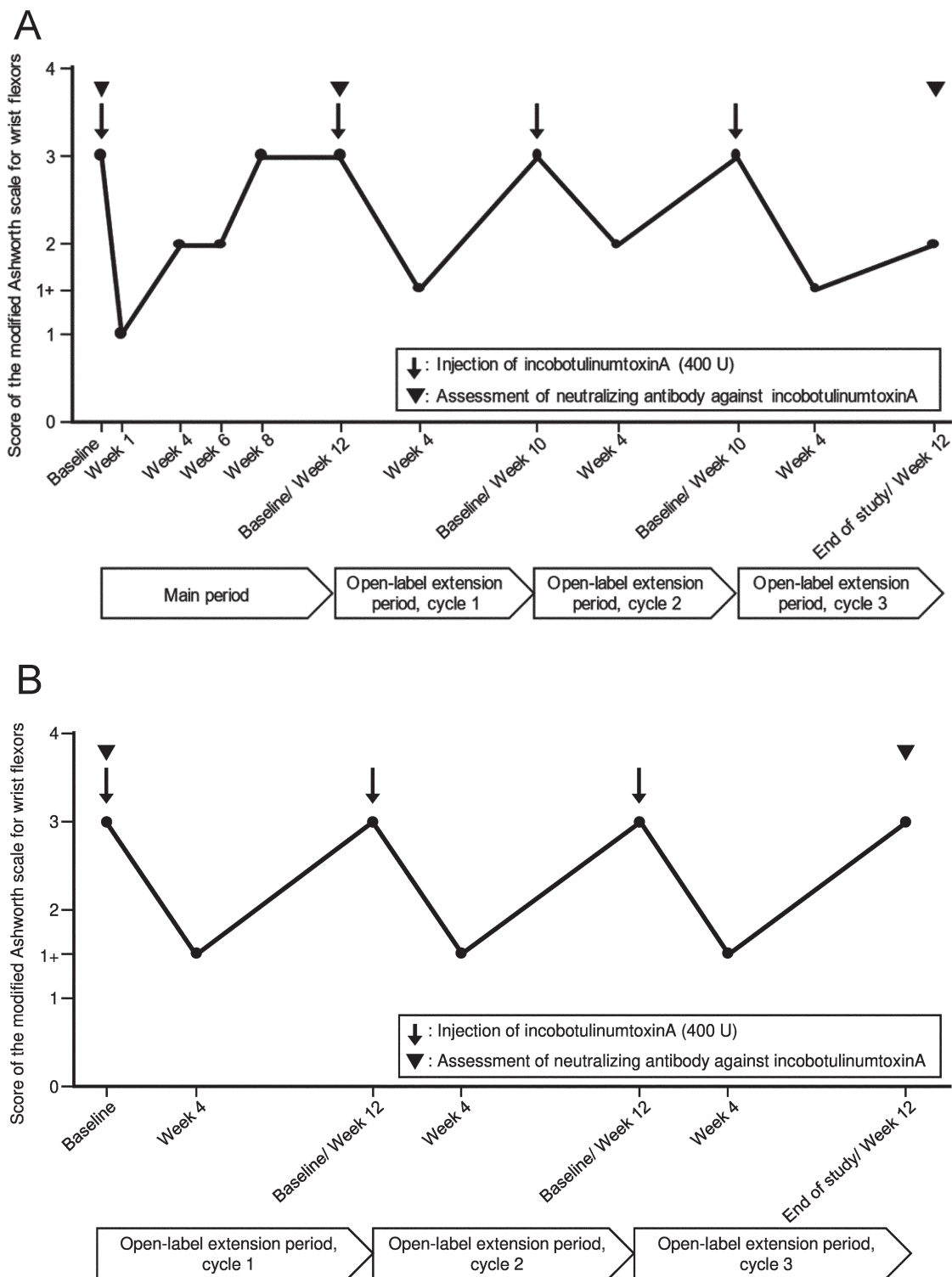


Fig. 1. IncobotulinumtoxinA injection cycles and changes in the modified Ashworth scale wrist flexor score for case A (A) and case B (B). The score “1+” of the modified Ashworth scale is indicated as “1.5”.

tion of incoBoNT/A and 98.0 min at study completion. No adverse events related to the incoBoNT/A injections were observed.

DISCUSSION

This case report describes responses as the reduction in MAS score after injections of 400 U incoBoNT/A in the presence of high titers of neutralizing antibodies monitored using HDA. In the phase 3 study, all patients testing positive for neutralizing antibodies had been treated with onaBoNT/A before the study. In one study on post-stroke spasticity, a patient who had experienced secondary failure after 1 year of treatment with BoNT/A containing complexing proteins showed a good efficacy response after switching to incoBoNT/A several months after the failure.¹⁰ The failure of prior BoNT/A treatment was indirectly inferred to be antibody induced, based on the extensor digitorum brevis test; however, neutralizing antibody status during the incoBoNT/A treatment was not explicitly stated.¹⁰ For cervical dystonia, several studies about switching to incoBoNT/A in neutralizing antibody-positive patients have been reported.^{11–13} Neutralizing antibodies decrease or disappear over 3–10 years after the cessation of BoNT/A,^{11,12,14} and initiation of incoBoNT/A after the decline of neutralizing antibody titers has been recommended.¹¹ However, neutralizing antibodies induced by prior BoNT/A treatment decreased as rapidly during incoBoNT/A treatment as after the cessation of the BoNT/A treatment; efficacy response was concurrently observed in most patients after switching to incoBoNT/A.¹²

While this report sheds light on the efficacy of incoBoNT/A in neutralizing antibody-positive patients, the number of patients is small, and the immunological explanation for the observed effects in the presence of neutralizing antibodies against the core botulinum neurotoxin is insufficient. Therefore, further studies are warranted to evaluate the effectiveness of incoBoNT/A in the presence of neutralizing antibodies. The cases described here suggest that initiation of incoBoNT/A might be beneficial in neutralizing antibody-positive patients who were previously treated with the onaBoNT/A preparation.

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CONFLICTS OF INTEREST

YM has no conflicts of interest to declare. AD is an employee of Merz Pharmaceuticals GmbH. ST is an employee of Teijin Pharma Limited. RK's institution receives scholarship donations from Teijin Pharma Limited.

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