Long-Term Efficacy and Safety of OnabotulinumtoxinA in Patients with Neurogenic Detrusor Overactivity Who Completed 4 Years of Treatment

Eric Rovner,*,† Alfred Kohan,‡ Emmanuel Chartier-Kastler,§ Klaus-Peter Jünemann,‖ Giulio Del Popolo,¶ Sender Herschorn,** Manher Joshi,†† Andrew Magyar†† and Victor Nitti‡‡

From the Department of Urology, Medical University of South Carolina, Charleston, South Carolina (ER), Advanced Urology Centers of New York, Bethpage, New York (AK), Department of Urology, Pitié-Salpétrière Academic Hospital, University Paris 6, Paris, France (EC-K), Department of Urology and Pediatric Urology, Klinik für Urologie und Kinderurologie, Universitätsklinikum Schleswig-Holstein, Kiel, Germany (K-PJ), Department of Neurourology, Careggi University Hospital, Florence, Italy (GDP), Division of Urology, University of Toronto, Toronto, Ontario, Canada (SH), Allergan plc, Irvine, California (MJ), Allergan plc, Bridgewater, New Jersey (AM), and Department of Urology, New York University School of Medicine, New York, New York (VN)

Purpose: We assessed the year-to-year consistency of outcomes in patients with urinary incontinence due to neurogenic detrusor overactivity who completed 4 years of onabotulinumtoxinA treatment.

Materials and Methods: Eligible patients who completed a 52-week phase 3 trial of onabotulinumtoxinA for urinary incontinence could enter a 3-year open label extension study of onabotulinumtoxinA 200 or 300 U administered as needed for symptom control. This analysis focused on 227 patients who completed the 4-year study. Outcomes assessed by year of treatment included mean treatments per year, mean change from baseline at week 6 in urinary incontinence episodes per day and the I-QOL (Incontinence Quality of Life) total summary score, the proportion of patients with 50% or greater and 100% reductions in urinary incontinence episodes per day, duration of effect and adverse events.

Results: Patients reported 4.3 urinary incontinence episodes per day at baseline and received 1.4 to 1.5 onabotulinumtoxinA treatments per year. The decrease in urinary incontinence following onabotulinumtoxinA consistently ranged from

Abbreviations and Acronyms

ACH = anticholinergic
AE = adverse event
CIC = clean intermittent catheterization
DOE = duration of effect
MS = multiple sclerosis
NDO = neurogenic detrusor overactivity
QOL = quality of life
SCI = spinal cord injury
UI = urinary incontinence
UTI = urinary tract infection

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* Correspondence: Medical University of South Carolina Health Urology Services, 96 Jonathon Lucas St., CSB 644, Charleston, South Carolina 29429 (telephone: 843-792-8347; FAX: 843-792-8523; e-mail: rovnere@musc.edu).

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†† Employees of Allergan plc and were employees at the time the work was conducted.

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−3.4 to −3.9 episodes per day across 4 years. A high proportion of patients achieved 50% or greater and 100% urinary incontinence reductions in each year (range 86.6% to 94.1% and 43.6% to 57.4%, respectively). Consistent and clinically relevant improvements in I-QOL scores were observed in each treatment year. The overall median duration of effect of onabotulinumtoxinA was 9.0 months or greater (range 3.0 to 49.2) and 26.0% or more of patients experienced a duration of effect of 12 months or greater. The most common adverse event was urinary tract infection with no increased incidence with time.

Conclusions: Patients with neurogenic detrusor overactivity who completed 4 years of onabotulinumtoxinA treatment experienced a consistent duration of treatment effect and year-to-year improvements in urinary incontinence and quality of life with no new safety signals.

Key Words: urinary bladder, neurogenic; onabotulinumtoxinA; urinary incontinence; quality of life; urinary tract infections

ONABOTULINUMTOXINA is approved for UI due to NDO in patients who have been inadequately treated with a ACH, according to manufacturer prescribing information. This approval was based on the results of 2 large, randomized, double-blind, placebo controlled, 52-week, phase 3 trials in patients with NDO and MS or SCI, which demonstrated that onabotulinumtoxinA provided statistically significant reductions in the number of UI episodes and improvements in QOL compared with placebo.[1,2]

Patients who completed the phase 3 studies were eligible to enter a prospective, multicenter, 3-year, open label extension study to establish the long-term efficacy of onabotulinumtoxinA for NDO. To our knowledge the combined 4-year study duration represents the largest long-term prospective assessment of any active treatment for NDO. The initial study analysis demonstrated that long-term repeat onabotulinumtoxinA treatment consistently improved UI, volume per void and QOL with no new safety signals for up to 4 years.[3,4] However, assessments of treatment response are often limited in long-term studies by discontinuation rates.

To assess safety and efficacy outcomes in patients who persisted on onabotulinumtoxinA therapy for a full 4 years of treatment we performed a post-hoc analysis of patients who completed this long-term extension study. Because all patients received 4 years of treatment and requested re-treatment as needed, the total number of treatments received during the study differed among patients. To account for this we evaluated outcomes by year instead of by treatment cycle.

MATERIALS AND METHODS

Patient Selection and Study Design

Data from 2 phase 3 studies and the associated extension study were pooled for analysis. Details of patient selection and study design have been previously described.[1–4] Briefly, eligible patients with NDO and MS or SCI inadequately managed by a ACH had completed 1 of 2, 52-week phase 3 studies[1,2] before enrolling in the 3-year multicenter, multinational, open label extension study.[3,4] In the initial phase 3 studies patients could receive up to 2 onabotulinumtoxinA treatments consisting of 200 or 300 U administered via cystoscopy as 30, 1 ml intradetrusor injections and avoiding the trigone. During the extension study patients could then request re-treatment as needed for symptom control so that the number of treatments received by each patient varied. Patients had to request re-treatment and fulfill prespecified criteria (1 or more UI episodes within 3 days and 12 or more weeks since previous treatment) before they could receive re-treatment.

During the course of the extension study no clinically relevant differences in efficacy were observed between the 200 and 300 U doses of onabotulinumtoxinA. Therefore, the 200 U dose was put forth for FDA (Food and Drug Administration) approval. Thus, patients originally received the same dose of onabotulinumtoxinA that they received in the phase 3 studies. After FDA regulatory approval of the 200 U dose the protocol was amended so that all patients received only 200 U for the remainder of the extension study. The current analysis focuses only on patients who completed the entire 4 years of treatment.

Study Outcomes

Efficacy assessments included the change from study baseline in UI episodes per day as the primary efficacy end point and I-QOL total summary scores at week 6 after each treatment. The baseline value of each study outcome was defined as the value immediately before the first treatment in the phase 3 studies. Additional assessments included the proportion of patients with 50% or greater and 100% reductions in UI episodes per day, DOE (defined as time to the patient request for re-treatment) and AEs.

UTIs were defined as a positive urine culture with a bacteriuria count of greater than 10^5 cfu/ml and leukocyturia greater than 5 per high power fields or a positive urine culture that required antibiotic therapy in the investigator opinion. Patients were not required to be symptomatic. Urinary retention was not defined in the protocol but rather determined by clinical judgment/physician discretion, as was the decision to initiate CIC.