Long-term Efficacy and Safety of OnabotulinumtoxinA in Patients With Urinary Incontinence Due to Neurogenic Detrusor Overactivity: An Interim Analysis

Michael Kennelly, Roger Dmochowski, Karen Ethans, Gilles Karsenty, Heiner Schulte-Baukloh, Brenda Jenkins, Catherine Thompson, Daniel Li, and Cornelia Haag-Molkenteller

OBJECTIVE To evaluate the long-term efficacy and safety of repeat onabotulinumtoxinA injections in patients inadequately managed by anticholinergics for urinary incontinence (UI) due to neurogenic detrusor overactivity.

MATERIALS AND METHODS Patients who completed either of 2 preceding phase III studies were offered entry into an extension study and received repeat onabotulinumtoxinA 200 U or 300 U. The data were integrated across the phase III and ongoing extension studies. The present interim analysis included all patients who received ≥1 onabotulinumtoxinA treatment. The data were analyzed by treatment cycle (cycles 1-5). The primary assessment was the change from baseline in UI episodes/wk at 6 weeks after each treatment. Additional assessments included ≥50% and 100% reductions in UI episodes, volume/void, Incontinence Quality of Life responses, and adverse events.

RESULTS A total of 387, 336, 241, 113, and 46 patients received 1, 2, 3, 4, and 5 onabotulinumtoxinA treatments, respectively. The UI episodes/wk were consistently reduced compared with baseline after repeated onabotulinumtoxinA treatment (−22.7, −23.3, −23.1, −25.3, and −31.9 for the 200-U onabotulinumtoxinA group in cycles 1-5). The proportion of patients reporting ≥50% and 100% ("dry") reductions from baseline in UI episodes at week 6 ranged from 73%-94% and 36%-55%, respectively. Increases in the mean volume/void (mean increase >130 mL) and improvements in quality of life were also observed after repeat treatment. The most common adverse events were urinary tract infections and urinary retention, with no change in the adverse event profile over time.

CONCLUSION The results of our study have shown that repeated onabotulinumtoxinA treatments provide sustained reductions in UI episodes and increases in the volume/void and quality of life in patients with neurogenic detrusor overactivity and UI who were inadequately managed by anticholinergics, with no new safety signals. UROLOGY 81: 491−497, 2013. © 2013 Elsevier Inc. Open access under CC BY-NC-ND license.

The clinical benefits of onabotulinumtoxinA (BOTOX, Allergan, Irvine, CA) for the treatment of urinary incontinence (UI) due to neurogenic detrusor overactivity (NDO) in patients who were not adequately managed by anticholinergics were first demonstrated in 2000 by Schurch et al.[1] These initial results were recently confirmed by 2 pivotal, phase III, randomized, placebo-controlled, double-blind trials.[2,3] Both phase III studies demonstrated that onabotulinumtoxinA, administered at a dose of 200 U and 300 U, significantly reduced UI episodes and improved the urodynamic parameters and quality of life (QOL) in patients with NDO and UI due to spinal cord injury (SCI) or multiple sclerosis (MS) who were inadequately managed by anticholinergics (inadequate efficacy or intolerable side effects). No clinically relevant differences in efficacy or duration of effect were observed between the 200 U and 300 U onabotulinumtoxinA doses, with efficacy lasting approximately 9-10 mo/injection. Where approved, the

Financial Disclosure: *Writing assistance for manuscript development was provided by Linda Wychowski, Ph.D., and Jaya Kolipaka, M.S., of Evidence Scientific Solutions and was funded by Allergan, Inc.; M. Kennelly, R. Dmochowski, K. Ethans, G. Karsenty, and H. Schulte-Baukloh have consulted for, conducted studies funded by, or received honoraria from Allergan, Inc.; and B. Jenkins, C. Thompson, D. Li, and C. Haag-Molkenteller are employees of Allergan, Inc.*

Funding Support: *This study and its analysis were funded by Allergan, Inc.*

From the Carolinas Rehabilitation, Charlotte, NC; Vanderbilt University, Nashville, TN; University of Manitoba, Winnipeg, Manitoba, Canada; Aix-Marseille Université, Marseille, France; St. Hedwig-Krankenhaus, Charité Universitätsmedizin Berlin, Berlin, Germany; Allergan, Inc., Irvine, CA; and Allergan, Ltd., Marlow, United Kingdom

Reprint requests: Michael Kennelly, M.D., F.A.C.S., Department of Urology, Carolinas Rehabilitation, 1100 Blythe Boulevard, Charlotte, NC 28203. E-mail: Michael.Kennelly@carolinashealthcare.org

Submitted: June 27, 2012, accepted (with revisions): November 6, 2012

© 2013 Elsevier Inc. Open access under CC BY-NC-ND license.

http://dx.doi.org/10.1016/j.urology.2012.11.010

200-U dose of onabotulinumtoxinA is the registered dose for the treatment of patients with UI due to NDO. OnabotulinumtoxinA is not interchangeable with other botulinum toxin preparations.

To evaluate the efficacy and safety of repeat injections of onabotulinumtoxinA in patients with UI due to NDO resulting from SCI and MS, a prospective, long-term, open-label, extension study of the phase III clinical trials was initiated, with patients able to participate for up to 3 years. This extension study is still ongoing. In the present study, we report an interim analysis of the results from the extension study, focusing on the results of repeated treatment for up to 5 treatment cycles.

MATERIAL AND METHODS

Patients and Study Design

Details regarding patient selection and the study designs of the pivotal phase III trials (the Double-blind InvestiGation of purified NeurotoxIn complex in neurogenic deTrusorover-activitY [DIGNITY] studies) have been previously published (http://www.clinicaltrials.gov identifiers NCT00311376 and NCT00461292).[2,3] In brief, the studies enrolled patients aged ≥18 years who had NDO due to SCI or MS with ≥14 UI episodes/wk and who were not adequately managed by anticholinergics (inadequate efficacy or intolerable side effects). Patients who were taking anticholinergics at study entry continued to take them during the remainder of the 52-week phase III trials. Patients who completed either of the phase III studies could enter the long-term, 3-year extension study, in which they would receive multiple intradetrusor treatments of onabotulinumtoxinA (http://www.clinicaltrials.gov identifier NCT00876447). All patients provided written informed consent, and each participating center obtained institutional review board or ethics committee approval.

The dose of onabotulinumtoxinA that patients received during the extension study was the same as the dose the patient had been randomized to receive in the preceding phase III studies (200 U or 300 U). The study protocol was amended in March 2011 such that all patients would receive onabotulinumtoxinA 200 U (the registered dose for NDO, where approved) regardless of whether they had received 200 U or 300 U in the preceding phase III studies. However, the interim data we report presents the results for both the 200-U and the 300-U dose groups (ie, the dose to which patients had been randomized in the phase III studies and also received in the extension study before the amendment).

Just as in the phase III trials, treatment was administered as 30 injections of 1 mL using cystoscopy (avoiding the trigone) with either no anesthesia, local anesthesia (with or without sedation according to local site practice), or general anesthesia. Patients could receive repeat treatment if the prespecified repeat treatment criteria had been fulfilled. These included patient initiation of a request for repeat treatment, a minimum of 12 weeks since the previous study treatment, and ≥1 UI episode within 3 days, as recorded in the 3-day patient diary before a study visit.

Safety and Efficacy Assessments

Patients recorded each voiding episode (UI, toilet void, clean intermittent catheterization [CIC] void) in a bladder diary in the week preceding each study visit. For one 24-hour period, the volume of each void was also measured. The patients were evaluated at weeks 2, 6, and 12 after each treatment.

The primary efficacy measure was the change from study baseline in the number of weekly UI episodes. The prespecified primary point of assessment in each cycle was week 6 after each treatment, identical to the endpoint in the pivotal studies. Baseline was defined as the value before any study treatment in the preceding phase III studies. Additional efficacy variables at week 6 after each treatment included the proportion of patients with ≥50% and 100% reductions from baseline in UI episodes, a change from baseline in the Incontinence Quality of Life (I-QOL) total summary scores,[4] the I-QOL responder rates (proportion of patients achieving a ≥11-point increase from baseline in I-QOL score), the duration of treatment effect (interval to patient request for repeat treatment), and the mean volume/void.

Adverse events (AEs) were also assessed. Urinary tract infections (UTIs, as reported by the investigators), were defined as positive urine culture results with a bacteriuria count of $>10^5$ colony-forming units/mL in conjunction with a leukocyturia of >5/high powered field or positive urine culture findings that, in the investigator's opinion, required antibiotic therapy. Symptomatic and asymptomatic UTIs were not distinguished. No predefined definition was in place for urinary retention in the study protocol. Therefore, the interpretation of recording urinary retention as an AE and the need for the initiation of CIC after treatment were determined by the investigator's clinical judgment.

The presence of serum neutralizing antibodies was assessed using the mouse protection assay[5] at baseline (in the preceding phase III studies), before each treatment, and at study exit.

Statistical Analysis

The long-term extension study had no formal statistical power or sample size calculation because only patients from the preceding phase III studies could be enrolled. The data from the patients in the interim analysis of the long-term extension study were integrated with the corresponding data from the preceding phase III studies. All patients who received ≥1 onabotulinumtoxinA treatment were included. The data were analyzed by onabotulinumtoxinA treatment cycle. The present report presents the efficacy and safety results from an interim analysis covering 5 treatment cycles.

Efficacy and safety analyses were conducted using the onabotulinumtoxinA-treated population. The mean changes from baseline with 95% confidence intervals were calculated for all efficacy variables. Because the long-term study used 3-day bladder diaries, weekly UI was calculated as the daily frequency of incontinence episodes multiplied by 7. Missing values for I-QOL measures were imputed from multi-item scales. The duration of treatment effect for each treatment cycle was calculated according to those patients who requested repeat treatment (and their repeat treatment request date) and was summarized using descriptive statistics. De novo (ie, first time) catheterization rates for patients not using CIC at baseline in the phase III studies were calculated for each treatment cycle. The denominator represented the number of patients who received onabotulinumtoxinA in the applicable cycle and had never initiated CIC before receiving treatment in that cycle, and the numerator represented the number of patients who initiated CIC for the first time during that cycle.

Download English Version:

https://daneshyari.com/en/article/6167508

Download Persian Version:

https://daneshyari.com/article/6167508

Daneshyari.com