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Early and Consistent Improvements in Urinary Symptoms and Quality of Life With OnabotulinumtoxinA in Patients With Overactive Bladder and Urinary Incontinence: Results From a Randomized, Placebo-controlled, Phase IV Clinical Trial

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Objectives: This randomized, multicenter, placebo-controlled, phase IV study assessed the efficacy and tolerability of onabotulinumtoxinA in patients with overactive bladder.

Methods: Patients were randomized 1:1 to onabotulinumtoxinA 100 U or placebo. Assessments over 12 weeks included: change from baseline in urinary incontinence (UI) episodes/day; proportions of patients who achieved 100% and 50% or greater reductions in UI episodes/day; proportion of patients using no incontinence pads in the previous 24 hours; and changes from baseline in micturition frequency, nocturia, urgency UI, Incontinence-Quality of Life, King's Health Questionnaire, International Consultation on Incontinence Questionnaire—UI Short Form scores and time to request retreatment.

Results: Significant reductions in UI episodes/day were seen with onabotulinumtoxinA versus placebo within week 1 posttreatment (−2.9 vs −2.0, $P = 0.005$) through week 12 (coprimary endpoint: −3.5 vs −1.6, $P < 0.001$). Significantly more onabotulinumtoxinA-treated patients achieved 100% (coprimary endpoint) and 50% or greater reductions in UI episodes/day. Decreases in other urinary symptoms were also seen within 1 week with onabotulinumtoxinA that continued through at least week 12. More onabotulinumtoxinA-treated versus placebo-treated patients required no incontinence pads at weeks 1 to 12, and greater improvements in quality of life measurements were seen. Time to request retreatment was significantly longer with onabotulinumtoxinA versus placebo (30.0 weeks vs 13.1 weeks; $P < 0.001$). No unexpected safety signals were observed. Urinary tract infection was the most commonly observed adverse event.

Conclusions: Urinary symptom and quality of life improvements were observed with onabotulinumtoxinA within 1 week of treatment and were sustained for at least 12 weeks.

Key Words: OnabotulinumtoxinA, overactive bladder, urinary incontinence, quality of life

(*Female Pelvic Med Reconstr Surg* 2021;27: 450–456)

Overactive bladder (OAB) is a chronic condition characterized by urinary frequency and urgency, with or without urge incontinence.[1] Overactive bladder affects approximately 17% of the population and increases in prevalence with age.[2] Although OAB occurs at similar rates in men and women, women experience higher rates of OAB with urge incontinence.[2] OAB-associated urinary symptoms can have a profound negative effect on daily living, work productivity, and health-related quality of life (QOL).[3–5] Patients with OAB have higher rates of depression, less engagement in physical activity, and decreased enjoyment of sexual activity than the general population.[3–5]

In patients with OAB for whom first-line therapies are inadequate, available second-line pharmacologic therapies include oral medications, such as anticholinergic agents and mirabegron, a beta-3 agonist.[6] However, over 12 months, both mirabegron and anticholinergics have relatively high discontinuation rates (67% and 84%, respectively),[7] and recently, the cumulative use of anticholinergic medications has been documented to be associated with an increased risk for cognitive impairment.[8,9]

OnabotulinumtoxinA (BOTOX; Allergan plc, Dublin, Ireland) is approved as a third-line treatment option for patients with OAB who have an inadequate response to, or are intolerant of, an anticholinergic medication. Beta-3 agonists became available after phase III development of onabotulinumtoxinA commenced and so the phase III trials only included those who failed anticholinergics. Randomized, placebo-controlled, multicenter phase III trials with onabotulinumtoxinA 100 U demonstrated significant improvements in urinary incontinence (UI), other urinary symptoms, and QOL.[10–12] For example, 23% to 34% of OAB patients were completely continent 12 weeks after onabotulinumtoxinA 100 U treatment.[11,12] An extension study of 2 of the phase III trials found a median time to request retreatment of 7.6 months.[13] OnabotulinumtoxinA was generally well tolerated in these trials, with an increased risk versus placebo for urinary tract infection (UTI) and clean intermittent catheterization (CIC),

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This article published online ahead of print on July 13, 2020.
Conflicts of Interest and Source of Funding: This study and its analysis were sponsored by Allergan plc, Dublin, Ireland. Medical writing and editorial assistance was provided by Jennifer L. Giel, PhD, CMPP, and Karen Pemberton, PhD, CMPP, on behalf of Evidence Scientific Solutions, Inc., Philadelphia, PA, and was funded by Allergan plc, Dublin, Ireland.
All authors met the ICMJE authorship criteria. Neither honoraria nor payments were made for authorship. Kurt McCammon has served as a consultant/advisor and meeting participant/lecturer for AMS and Solace; as study investigator for AMS, Allergan plc, Astellas, Solace, and Uroplasty; and is a board member/officer/trustee for IVUmed. Angelo Gousse has served as a consultant/advisor and investigator for Allergan plc and Precision Medical Devices. Alfred Kohan has been an investigator for Allergan plc, Ipsen, Myovant, and Watson; and a speaker for Allergan plc and Watson. David Glazier has been a study investigator for Allergan plc. Jennifer Gruenenfelder has served as a consultant and study investigator for Allergan plc. Zhanying Bai and Anand Patel are employees of Allergan plc. Douglass Hale has served as a consultant/advisor and meeting participant/lecturer and has received research funding from Allergan plc.
Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.fpmrs.net).

DOI: 10.1097/SPV.0000000000000914

required if predefined criteria were met for raised postvoid residual (PVR) urine volume.[10–12]

This phase IV placebo-controlled study was designed to lend support to the existing literature by assessing the relative efficacy and tolerability of onabotulinumtoxinA over 12 weeks in patients with OAB inadequately controlled with anticholinergic medications. Furthermore, this study was unique in that treatment responses were collected within the first week allowing for earlier assessment of onset and magnitude of efficacy.

MATERIALS AND METHODS

Study Design and Patients

This randomized, multicenter, placebo-controlled, phase IV, postmarketing trial (ClinicalTrials.gov registry number NCT01945489) was conducted at 44 sites in the United States between November 2013 and January 2017. Eligible patients were adults who had OAB for 6 months or longer, were inadequately managed by an anticholinergic, and had recorded 3 or more episodes of urgency UI (UUI), 1 or less UUI-free day, and 24 or greater micturitions on a 3-day paper bladder diary during screening. Key exclusion criteria included OAB caused by any neurologic condition; predominance of stress UI, surgery, or disease other than OAB that might affect bladder function; PVR greater than 100 mL; and a 24-hour total urine void volume greater than 3000 mL during screening. Anticholinergic use or any other therapy to treat symptoms of OAB was not permitted within 7 days of screening or throughout the study.

Patients were randomized (1:1) via an interactive voice response/interactive web response system to onabotulinumtoxinA 100 U or placebo administered as 20 injections (0.5 mL each) via cystoscope into the detrusor, avoiding the trigone, consistent with the phase III studies and the indication according to the US Food and Drug Administration. Patients could request and receive retreatment with open-label onabotulinumtoxinA 100 U if they fulfilled the prespecified retreatment criteria: (1) 12 weeks or longer had elapsed since the previous administration of the study drug, (2) the patient experienced 2 or more UUI episodes and 1 or less UUI-free day according to a 3-day bladder diary in the week before retreatment qualification, (3) the patient had a PVR urine volume less than 200 mL, and (4) the investigator deemed retreatment appropriate.

The study protocol was approved at each study site by an ethics committee or institutional review board, the study was conducted in accordance with Good Clinical Practice, and all patients provided written informed consent.

Assessments

Efficacy

A paper bladder diary, completed over 3 consecutive days at any time in the week before the visit, was used to assess OAB symptoms (UI, micturition, nocturia, UUI). The bladder diary and additional assessments for efficacy and QOL were performed at all visits (weeks 1 [±3 days], 2 [±3 days], 6 [±7 days], and 12 [±7 days]).

Coprimary endpoints were (i) mean change from baseline in UI episodes/day and (ii) proportion of patients achieving 100% reduction in UI episodes/day (complete continence) at week 12 after treatment.

Secondary endpoints included: mean King's Health Questionnaire (KHQ) domain scores for 2 of the 7 multi-item domains ("Role Limitations" and "Social Limitation"), number of micturition episodes, nocturia episodes, and reduction in UUI episodes/day.

Other endpoints included: the proportion of patients achieving 50% or greater reduction in UI episodes/day and the proportion of patients using no incontinence pads in the previous day. Several QOL endpoints, each validated for use in men and women, were also evaluated. These included change from baseline in the remaining 5 of the 7 multi-item domains of the KHQ (Physical Limitations, Personal Relationships, Emotions, Sleep/Energy, and Severity [Coping]) and an additional single-item domain (Incontinence Impact). The KHQ specifically evaluates QOL in patients with lower urinary tract conditions including OAB[14]; domain scores range from 0 to 100 (lower score indicates better QOL). Proportions of patients achieving the minimally important difference (MID)[15,16] of −5 points in KHQ Role and Social Limitations domains were also included. Other QOL endpoints evaluated were (1) change from baseline in incontinence (I)-QOL total and domain scores (avoidance and limiting behavior, psychosocial impact, and social embarrassment), a UI-specific questionnaire with scores ranging from 0 to 100 (higher score indicates better QOL),[17,18] and (2) change from baseline on the International Consultation on Incontinence Questionnaire–Urinary Incontinence (ICIQ-UI) Short Form score, a 4-item questionnaire that assesses the frequency, severity, and impact on QOL of UI.[19] Time to request retreatment was also recorded.

Safety

Adverse events (AEs) occurring during the 12 weeks after treatment were assessed. Urinary tract infection was defined as a bacteriuria count $>10^5$ colony-forming units/mL and leukocyturia >5 cells/high-powered field, regardless of symptoms. Urinary retention was defined as an increased PVR urine volume 200 or greater to less than 350 mL with associated symptoms (eg, voiding difficulties, sensation of bladder fullness) assessed by the investigator to require CIC, or 350 mL or greater regardless of symptoms. Clean intermittent catheterization was initiated if these PVR urine volume criteria for urinary retention were met, consistent with the phase III trials.

Statistical Analysis

Sample size was determined using data from the registrational phase III trials of onabotulinumtoxinA in OAB patients.[10,12] Data from 109 patients per group gave 90% power to detect a between-group difference in proportions achieving 100% UI reduction, assuming a 2-sided, continuity-corrected χ^2 test at alpha = 0.05 and 95% power to detect a between-group difference of 1.7 in change from baseline in UI episodes at week 12 (assuming a common standard deviation of 3.46 episodes and a 2-sided type I error rate of 0.05 using the 2-sample *t* test, for a joint power ≥ 0.85). These values were estimated based on the results from the 2 pivotal phase 3 studies (ClinicalTrials.gov: NCT00910845 and NCT00910520).[10,12] To address possible attrition (estimated to be 15%), the sample size was increased to 129 patients per group.

Efficacy and QOL endpoints were analyzed at weeks 1 through 12 after treatment in the intent-to-treat population (all randomized patients). Change from baseline in UI episodes, micturition episodes/day, nocturia episodes/night, UUI episodes/day, KHQ domain scores, I-QOL scores, and ICIQ-UI short form scores were analyzed using analysis of covariance with stratification and baseline value as covariates and treatment as a factor. Proportions of patients achieving 100% or 50% or greater reduction in UI episodes or achieving/exceeding the MID for KHQ Role and Social Limitations domains were analyzed using the

Cochran-Mantel-Haenszel method stratified by baseline UUI episodes of 9 or less versus greater than 9. Missing values for UI episodes, micturition episodes/day, nocturia episodes/night, and UUI episodes/day were imputed using last observation carried forward at the follow-up visit. I-QOL subscores were transformed to a scale of 0 to 100. Time to request retreatment was analyzed with the Kaplan-Meier method and the log-rank test stratified by baseline UUI. The safety population consisted of all patients who received study drug.

RESULTS

Patient Characteristics and Disposition

A total of 129 patients were randomized to onabotulinumtoxinA 100 U and 125 to placebo (see Figure, Supplemental Digital Content 1, http://links.lww.com/FPMRS/A148, which shows patient disposition). The impact of the omitted data on the overall efficacy results analysis was considered to be minimal. The number of patients with missing data was small (7/254 or 2.8% of total study population) and the omitted data for any individual patient was confined to a single assessment time point. Two patients (1 in the onabotulinumtoxinA arm and 1 in the placebo arm) had omitted data at the week 12 primary assessment time point.

Baseline demographics and disease characteristics were balanced between treatment groups (Table 1) and similar to previous phase III studies.[10,12] The vast majority of the study population was female (89%), and mean duration of OAB was longer than 9 years.

TABLE 1. Demographics and Baseline Disease Characteristics (ITT Population)

	OnabotA 100 U (n = 129)	Placebo (n = 125)	Total (N = 254)
Age, y	60.8 (12.7)	60.9 (12.1)	60.8 (12.4)
<65, n (%)	75 (58.1)	74 (59.2)	149 (58.7)
≥65, n (%)	54 (41.9)	51 (40.8)	105 (41.3)
Sex, female, n (%)	114 (88.4)	112 (89.6)	226 (89.0)
Weight, kg	88.9 (21.2)	89.2 (21.1)	89.1 (21.1)
Duration of OAB, y	9.3 (9.7)	9.6 (10.7)	9.4 (10.2)
UI episodes/day	5.4 (3.2)	6.0 (3.8)	5.7 (3.5)
UUI episodes/day	4.9 (3.1)	5.3 (3.5)	5.1 (3.3)
Micturition episodes/day	10.2 (3.0)	11.1 (3.4)	10.6 (3.2)
Nocturia episodes/night	2.2 (1.4)	2.1 (1.4)	2.2 (1.4)
PVR urine volume, mL*	16.8 (25.8)	17.9 (23.5)	17.4 (24.7)
KHQ			
Role limitations	70.7 (27.5)	72.0 (29.4)	71.3 (28.4)
Social limitations	43.7 (28.9)	46.8 (32.1)	45.2 (30.5)
Physical limitations	66.4 (29.7)	64.9 (30.1)	65.7 (29.8)
Personal relationships†	42.9 (35.0)	43.2 (36.6)	43.1 (35.7)
Emotions	52.4 (31.0)	53.6 (29.2)	53.0 (30.1)
Sleep/energy	71.4 (25.7)	71.0 (25.1)	71.2 (25.3)
Severity (coping)	65.7 (21.3)	69.2 (22.2)	67.4 (21.8)
Incontinence impact	85.7 (21.2)	86.6 (19.9)	86.1 (20.5)
I-QOL total summary score	35.2 (19.8)	33.8 (20.3)	34.5 (20.0)
Avoidance and limiting behavior	28.6 (17.0)	27.0 (17.3)	27.8 (17.1)
Psychosocial impact	41.2 (22.7)	40.6 (23.8)	40.9 (23.2)
Social embarrassment	23.0 (20.4)	20.7 (21.6)	21.9 (21.0)
ICIQ-UI Short-Form	14.6 (4.3)	14.8 (4.1)	14.7 (4.2)

Data are mean (SD) unless otherwise indicated.

*Safety population.

†OnabotA and placebo n values were 87 and 86, respectively.

ITT, intent-to-treat; onabotA, onabotulinumtoxinA.

Efficacy

Coprimary Endpoints

Significant reductions were seen from baseline in UI episodes/day with onabotulinumtoxinA versus placebo at week 12 (−3.5 vs −1.6; $P < 0.001$, Fig. 1A). These improvements were seen as early as within the first week (−2.9 vs −2.0; $P = 0.005$).

Nearly one third of onabotulinumtoxinA-treated patients (32.0%) were completely dry 12 weeks after treatment versus 7.2% with placebo (odds ratio 6.506; $P < 0.001$, Fig. 1B). One quarter of patients treated with onabotulinumtoxinA became completely dry within the first week (24.2%) versus 4.8% of those treated with placebo (odds ratio, 6.784; $P < 0.001$).

Secondary and Other Efficacy Endpoints

Urinary Symptoms

The proportion of patients with a 50% or greater reduction in UI episodes was higher in patients treated with onabotulinumtoxinA versus placebo at all measured time points between weeks 1 and 12 (Fig. 1C).

Significant reductions from baseline in the frequency of UUI, nocturia and micturition episodes were also seen at week 12 with onabotulinumtoxinA versus placebo; within the first week for UUI and nocturia episodes and by week 6 for micturition episodes (see Table, Supplemental Digital Content 2, http://links.lww.com/FPMRS/A147, which shows the change from baseline in other urinary symptoms).

Incontinence Product Use and Quality of Life

After treatment with onabotulinumtoxinA, there was a continual decrease in the need for incontinence pads (Fig. 2A). By week 12, nearly half of onabotulinumtoxinA-treated patients reported they had not required incontinence pads in the previous 24 hours, compared with a third of placebo-treated patients. This reduction in pad usage corresponded with decreases in KHQ Incontinence Impact scores, which were significantly lower for onabotulinumtoxinA-treated versus placebo-treated patients at weeks 2 to 12 (Fig. 2B). Improvements were reported at week 12 and as early as week 1 in the KHQ Role and Social Limitations domains that consistently exceeded the MID of −5 points[15] (Fig. 3A and B). Significantly higher proportions of onabotulinumtoxinA-treated vs placebo-treated patients achieved or exceeded the MID from weeks 1 through 12 for Role Limitations and from weeks 2 through 12 for Social Limitations (see Figure, Supplemental Digital Content 3, http://links.lww.com/FPMRS/A149 shows proportion of patients achieving or exceeding the MID for KHQ Role and Social limitations). Improvements in most of the other KHQ domain scores were significantly greater with onabotulinumtoxinA than placebo as early as week 1 through week 12 (see Figure, Supplemental Digital Content 4, http://links.lww.com/FPMRS/A150, which shows improvements in KHQ domain scores).

Early and sustained improvements were also observed in other QOL outcomes after onabotulinumtoxinA treatment versus placebo including I-QOL total summary score that exceeded the MID of 10 points[20] (Fig. 3C) and each of the 3 individual I-QOL subscales (see Figure, Supplemental Digital Content 5,

http://links.lww.com/FPMRS/A152, which shows improvement in I-QOL subscales).

In addition, at all time points out to week 12, changes from baseline in ICIQ-UI Short Form scores were significantly greater after onabotulinumtoxinA treatment versus placebo (Fig. 3D).

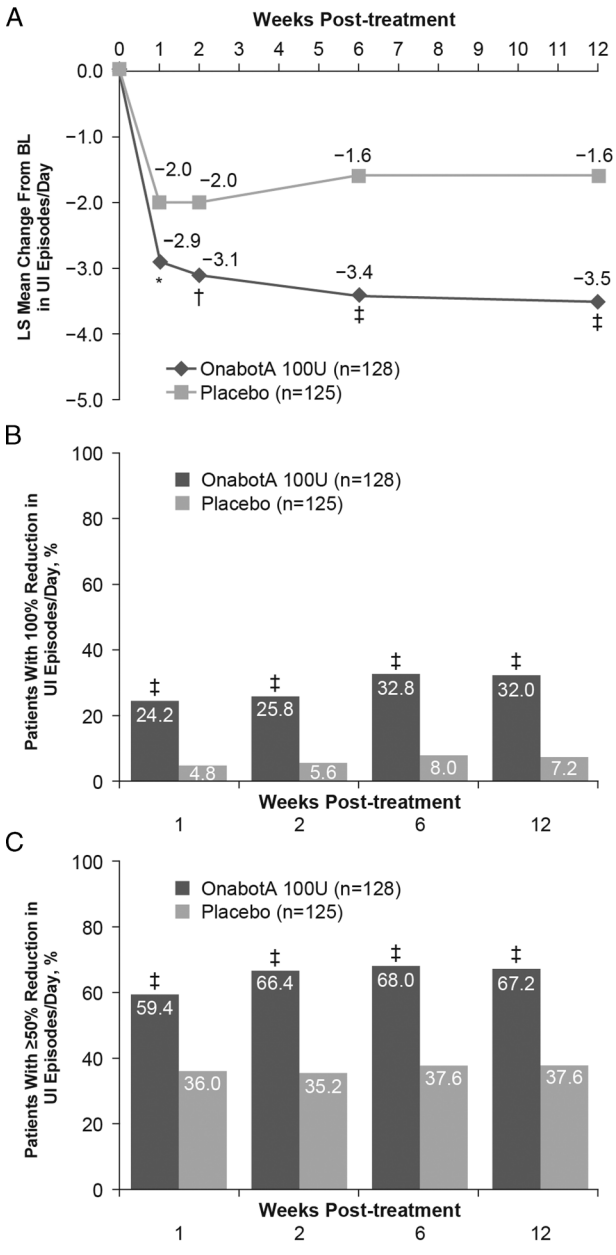

FIGURE 1. Improvement in UI episodes after treatment. A, LS mean change from BL. B, Proportion of patients with 100% reduction. C, Proportion of patients with ≥50% reduction. *$P = 0.005$; †$P = 0.003$; ‡$P < 0.001$ vs placebo. *P* values (A) were based on analysis of covariance with treatment as a factor and baseline value as a covariate. *P* values from (B) were from a Cochran-Mantel-Haenszel test adjusting for the randomization stratification factor (urinary incontinence at baseline: ≤9 episodes, >9 episodes). Missing values were imputed using last observation carried forward at the follow-up visits. LS, least squares; onabotA, onabotulinumtoxinA; BL, baseline.

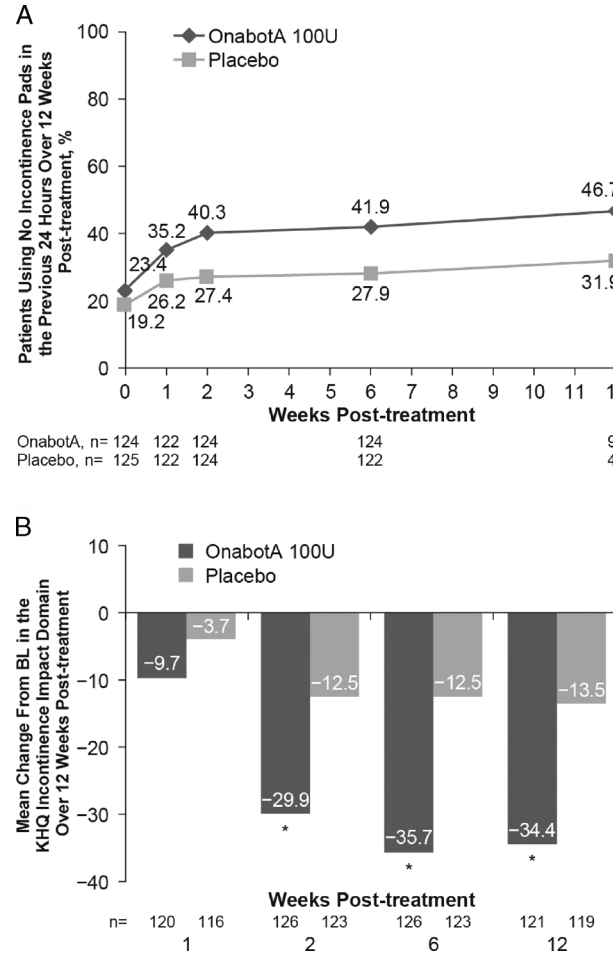

FIGURE 2. A, Proportion of patients using no incontinence pads in the previous 24 hours in the 12 weeks after treatment. B, Mean change from BL in the single-item domain for incontinence impact of the KHQ over 12 weeks after treatment. *$P < 0.001$ vs placebo. Note: Statistical comparisons not performed for pad use. N values denote the number of patients with data available at the evaluated time point.

Time to Request Retreatment

The time for patients to request retreatment was significantly longer with onabotulinumtoxinA (median [95% confidence interval], 30.0 [24.0–34.1] weeks) versus placebo (13.1 [12.4–14.4] weeks; $P < 0.001$).

Safety

In the 12 weeks after treatment, AEs were reported in 49.2% (63 of 128) and 33.6% (42 of 125) of patients in the onabotulinumtoxinA and placebo groups, respectively. Most AEs were mild or moderate in intensity. Urinary tract infections, urinary retention (both of which had protocol-defined reporting criteria), and dysuria were the most commonly reported AEs with onabotulinumtoxinA in the 12 weeks after treatment (Table 2). The majority of UTIs were mild to moderate in severity, and 1 was considered severe. One patient in the safety population discontinued the study as a result of an AE (urinary retention). Mean PVR urine volume was higher in onabotulinumtoxinA-treated than placebo-treated patients. Eight of 128 onabotulinumtoxinA-treated patients (6.3%) initiated CIC for urinary retention versus no

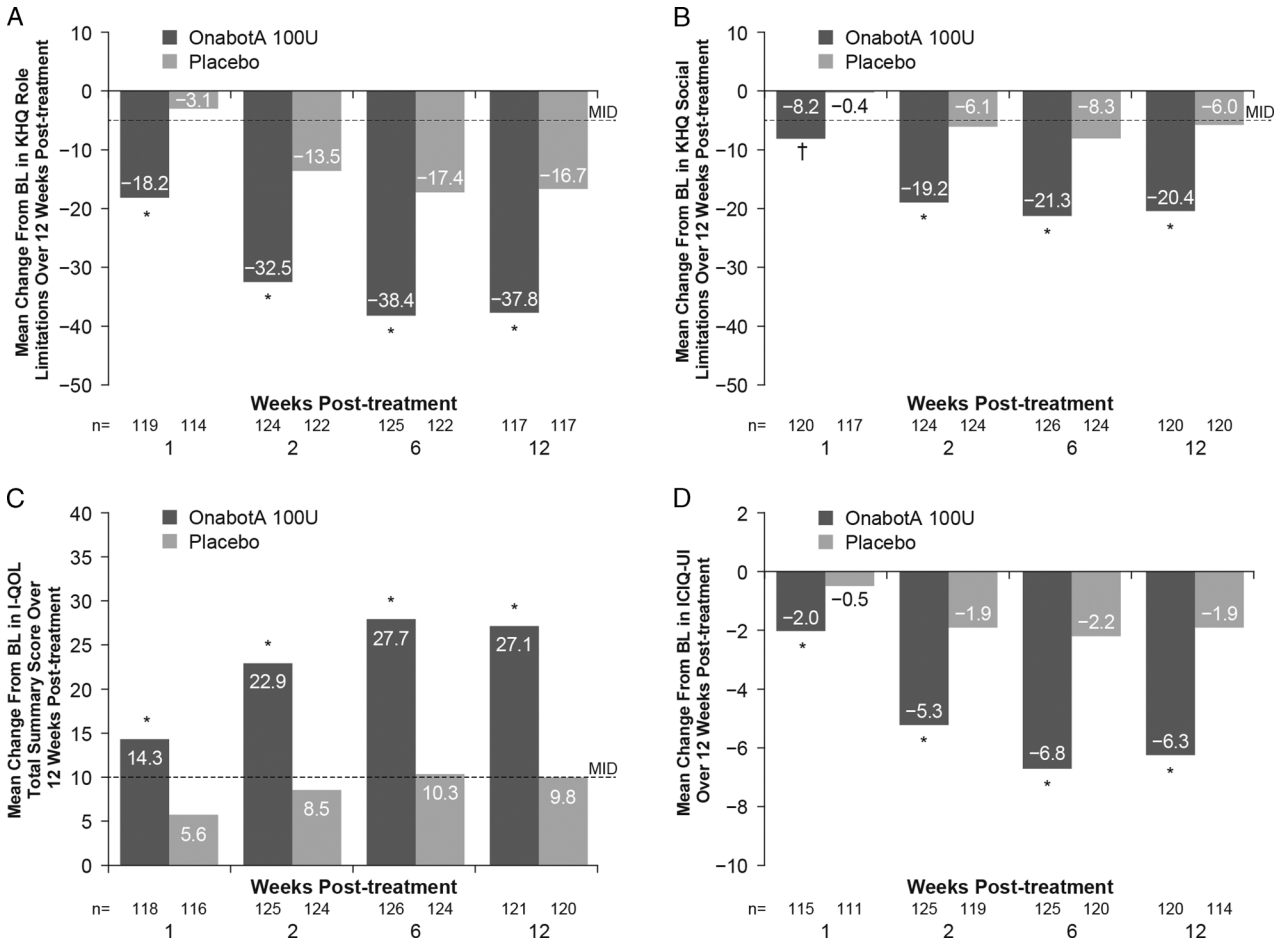

FIGURE 3. Quality-of-life improvements over 12 weeks after treatment. Mean change from BL in (A) KHQ role limitations, (B) KHQ social limitations, (C) I-QOL total summary score, and (D) ICIQ-UI after treatment up to week 12. *$P < 0.001$; †$P = 0.006$ vs placebo (KHQ, −5 points; I-QOL, 10 points) onabotA, onabotulinumtoxinA.

TABLE 2. Safety and Tolerability in the First 12 Weeks After Treatment

	OnabotA 100 U (n = 128)	Placebo (n = 125)
Treatment-emergent AEs >3%, n (%)		
UTI*	27 (21.1)	8 (6.4)
Urinary retention†	8 (6.3)	0
Dysuria	6 (4.7)	3 (2.4)
Bronchitis	1 (0.8)	4 (3.2)
Cough	0	4 (3.2)
CIC for urinary retention	8 (6.3)	0
Median CIC duration, d	78.5	–
Change from baseline in PVR urine volume, mean (SD)		
Week 2	56.6 (103.0)/n = 127	8.7 (38.8)/n = 125
Week 6	44.9 (73.7)/n = 126	6.8 (38.4)/n = 124
Week 12	33.9 (60.3)/n = 120	12.6 (38.6)/n = 120

*Defined as a positive urine culture (bacteriuria count $>10^5$ colony-forming units/mL) and leukocyturia (>5/high-powered field), regardless of symptoms.

†Defined as PVR urine volume ≥ 350 mL regardless of symptoms or PVR urine volume ≥ 200 to <350 mL with associated symptoms that required CIC in the investigator's opinion.

placebo-treated patients (Table 2). Four of these patients had PVR urine volumes.

DISCUSSION

In this randomized, placebo-controlled, multicenter study in OAB patients, onabotulinumtoxinA 100 U treatment resulted in significant reductions from baseline to week 12 in UI as well as improvements in other urinary symptoms and QOL versus placebo. These results were consistent with other phase III studies.[10–12] The registrational phase III studies assessed endpoints beginning at week 2 and, therefore, it was unknown whether the patients in those trials experienced clinical benefit before that time.[10,12] However, a small dose-ranging study of onabotulinumtoxinA (50–150 U) did report numeric improvements in urgency or UUI episodes in most patients when a 3-day bladder diary was assessed at day 8.[21] Importantly, the present study is the first to demonstrate that improvements in almost all outcomes were clinically relevant and significantly greater with onabotulinumtoxinA versus placebo within the first week after treatment.

In this study, QOL was measured using multiple disease-specific instruments. The consistent improvements seen across QOL questionnaires that assess similar and/or overlapping components of QOL reinforce the study's findings. Significant improvements in UI occurring as early as week 1 after the initial onabotulinumtoxinA treatment were reflected in early and sustained significant increases in I-QOL total summary score. The change in I-QOL total summary scores achieved or exceeded the MID at every time point, indicating clinically meaningful improvement. These improvements also coincided with significant increases in ICIQ-UI Short Form scores.

The increase in the proportion of patients who did not need to rely on incontinence pads corresponded with improvements on the KHQ Incontinence Impact domain among patients treated with onabotulinumtoxinA and may be reflective of increased confidence gained through the reduction in incontinence episodes. These improvements could also be of significant economic benefit to patients. The enhancements to social and emotional areas including improved social and family interactions and decreased feelings of helplessness, embarrassment, and depression occurred as early as the first week after treatment with onabotulinumtoxinA, as evidenced by significantly reduced scores on the KHQ Social Limitations domain and increased scores on the I-QOL Psychosocial Impact and Social Embarrassment subscales. Likewise, enhanced capability to engage in daily activities was seen with onabotulinumtoxinA, indicated by early and sustained improvements in scores on both the I-QOL Avoidance and Limiting Behavior subscales and the KHQ Role Limitations domain in onabotulinumtoxinA-treated patients. The change in KHQ Social and Role Limitations domain scores also exceeded the MID at every time point, indicating clinically meaningful improvement in QOL and potentially reinforcing similar clinically meaningful increases on all 3 I-QOL subscales.

The long-term use of onabotulinumtoxinA has been supported by the results of an extension of the registrational phase III studies (3.5 years).[13] The time to request retreatment for onabotulinumtoxinA was on average 7.6 months (30.4 weeks) and was consistent with this study (30.0 weeks).

OnabotulinumtoxinA was well tolerated in this study. Safety findings were consistent with those seen in earlier studies.[10–12] The most common AEs reported with onabotulinumtoxinA-treated patients in this study were UTI, urinary retention, and dysuria in the first 12 weeks after treatment.

The CIC rates in onabotulinumtoxinA-treated patients were consistent with those reported in earlier studies.[10–12] Of note, patients in this study initiated CIC if they met predefined PVR urine volume criteria, which may or may not be clinically relevant in a real-world setting.

Unlike anticholinergics, onabotulinumtoxinA is physician-administered, thus reducing compliance issues. OnabotulinumtoxinA also has both an early onset with minimal burden on patients after the procedure.

Study Limitations

It is not possible to exactly determine when the effect of onabotulinumtoxinA commences because bladder diaries typically take from 3 to 7 days to complete; however, in this study, the 3-day diary entry for week 1 could potentially have captured data from the day after treatment. Furthermore, the results here pertain only to the population of this study which included patients with OAB and UI. While this study was not designed to address cost comparisons, side effects leading to discontinuation of onabotulinumtoxinA are low in comparison to anticholinergic medications in which greater than 90% of patients have been reported to discontinue treatment over 2 years for a combination of reasons.

CONCLUSION

This study in patients with OAB who were inadequately managed with anticholinergics showed significant reductions in urinary symptoms and clinically relevant improvements in QOL after treatment with onabotulinumtoxinA 100 U with almost a third of patients achieving complete continence at 12 weeks. Improvements in urinary symptoms were seen as early as within 1 week posttreatment. Pad usage decreased over 12 weeks, and it is presumed that this is the result of patients becoming more confident in their continence posttreatment. These benefits were sustained throughout the study with minimal burden and low risk of needing CIC.

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