International Journal of Urology (2015) 22, 1131–1137 doi: 10.1111/iju.12912

Original Article: Clinical Investigation

Impact of onabotulinumtoxinA on quality of life and practical aspects of daily living: A pooled analysis of two randomized controlled trials

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Abbreviations & Acronyms
CIC = clean intermittent catheterization
HRQOL = health-related quality of life
I-QOL = Incontinence Quality of Life
KHQ = King's Health Questionnaire
MID = minimally important difference
OAB = overactive bladder
OnabotA = onabotulinumtoxinA
TBS = Treatment Benefit Scale
UI = urinary incontinence
UTI = urinary tract infection
UUI = urgency urinary incontinence

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Received 25 March 2015; accepted 2 August 2015.
Online publication 22 September 2015

Objective: To evaluate the impact of onabotulinumtoxinA on individual domains of the quality of life questionnaires in a pooled analysis of two phase 3 trials in overactive bladder patients with urinary incontinence who were inadequately managed by ≥1 anticholinergic.
Methods: Patients received intradetrusor injections of onabotulinumtoxinA 100U (n = 557) or placebo (n = 548). The proportions of patients with a positive response (condition "greatly improved" or "improved") on the Treatment Benefit Scale, and changes in Incontinence Quality of Life scores and King's Health Questionnaire domain scores were analyzed in the overall population and subgroups with clean intermittent catheterization use and urinary tract infection status during the first 12 weeks of treatment. Responses to individual King's Health Questionnaire items were also assessed.
Results: Significantly greater proportions of onabotulinumtoxinA-treated patients achieved positive Treatment Benefit Scale response versus placebo (61.8% *vs* 28.0%; $P < 0.001$). OnabotulinumtoxinA showed significantly greater improvements versus placebo in Incontinence Quality of Life total (22.5 *vs* 6.6), Incontinence Quality of Life subscale scores and all domains of the King's Health Questionnaire. Notably, a similar trend was observed regardless of clean intermittent catheterization/urinary tract infection status. Additionally, onabotulinumtoxinA resulted in significantly greater improvements than the placebo in practical aspects of patients daily lives, including pad use, need to change undergarments, sleep, relationship with partner and work life/daily activities.
Conclusion: In overactive bladder patients with urinary incontinence, onabotulinumtoxinA 100U demonstrated significant improvements across the individual domains of the quality of life questionnaires, regardless of clean intermittent catheterization or urinary tract infection status, and provided a positive impact on practical aspects of patients' daily lives.

Key words: health-related quality of life, onabotulinumtoxinA, overactive bladder, patient-reported outcomes, urinary incontinence.

Introduction

OAB is a common condition prevalent in 12–17% of the population, and is defined as urinary urgency, usually accompanied by frequency and nocturia, with or without UUI.[1–5] OAB symptoms have a negative effect on patients' HRQOL, including decreased work productivity, sexual satisfaction and performance of routine daily tasks, poorer sleep quality and increased feelings of depression.[6–8]

First-line therapeutic options, such as behavioral modifications, bladder retraining and pad use, are often inadequate.[9,10] Pharmacological treatment with anticholinergic therapy is often discontinued because of insufficient efficacy or intolerable side-effects.[11–14] Thus, there is a need for alternative treatments that can effectively reduce the burden of OAB symptoms and improve HRQOL in patients who are inadequately managed by anticholinergic therapy.

Two large, placebo-controlled, phase 3 trials independently showed that onabotA significantly reduces all symptoms of OAB, including episodes of incontinence, urgency, micturition and nocturia, and improves HRQOL outcomes in OAB patients with UI who were inadequately managed by ≥1 anticholinergic.[15,16] This pooled analysis of the two trials had

the following aims: (i) assess all individual HRQOL domains/subscales in the overall population; (ii) evaluate whether use of CIC or the presence of UTI affects HRQOL outcomes or patient perception of treatment benefit; and (iii) assess specific items on self-reported patient questionnaires that have practical implications for patients' daily lives, including pad use, work life, relationship with partner, mental well-being and sleep quality.

Methods

Study design

Details on the two phase 3 placebo-controlled trials (ClinicalTrials.gov identifiers: NCT00910845 and NCT00910520) have been previously published.[15,16] Briefly, the two trials enrolled OAB patients (n = 1105) who had experienced ≥3 UUI episodes over a 3-day period and ≥8 micturitions per day. Patients were randomized 1:1 to receive 20 cystoscopic intradetrusor injections (0.5 mL/injection) of onabotA 100U or placebo, sparing the trigone. Patients participated in the study for 24 weeks, and could receive retreatment with onabotA 100U from 12 weeks onwards if requested by the patients and if they had ≥2 UUI episodes as recorded in a 3-day diary. Dosing and results reported in the present study are specific to onabotA. This formulation is not interchangeable with other botulinum toxin products, and Units cannot be converted using a dose ratio. All patients had been inadequately managed by ≥1 anticholinergic, and those with a predominance of stress UI were excluded.

In the phase 3 trials, the change from baseline at week 12 in UI episodes/day (co-primary endpoint) after treatment with onabotA, and changes from baseline in other OAB symptoms of urgency, micturition and nocturia were assessed as measures of clinical efficacy.[15,16] For this analysis, data were pooled from the two trials to assess patient-reported outcomes at week 12 after the first treatment.

Patient-reported outcome measures

Patients recorded their perception of treatment benefit at each post-treatment visit using the one-item TBS (co-primary endpoint), rating their condition as "greatly improved," "improved," "not changed" or "worsened."[17] The impact of OAB on patients' HRQOL was assessed at week 12 post-treatment using the following two validated patient questionnaires: the I-QOL Instrument[18] and the KHQ.[19]

The I-QOL is a self-administered, disease-specific, 22-item questionnaire designed to measure the impact of UI on patients' lives. It provides a total summary score (prespecified secondary endpoint) ranging from 0 to 100, with higher scores reflecting better HRQOL (sum of all 22 individual items) plus three of the following domain scores: Avoidance and Limiting Behavior, Psychosocial Impact and Social Embarrassment. The KHQ is an OAB-specific questionnaire designed to measure the impact of OAB on patients' HRQOL on the multi-item domains of Role Limitations (prespecified secondary endpoint), Social Limitations (prespecified secondary endpoint), Physical Limitations, Personal Relationships, Emotions, Sleep/Energy and Severity/Coping measures, and two single-item domains of General Health perception and Incontinence Impact. Symptom scores range from 0 to 100, with lower scores indicating better HRQOL. The predefined clinically relevant change from baseline (MID) in these HRQOL measures was based on published literature, and determined a priori as follows: a +10-point increase for the I-QOL and a −5-point decrease for the KHQ.[20,21] The practical impact of OAB symptom reduction on patients' daily lives was further investigated by assessing patient responses at week 12 post-treatment to specific questions on the KHQ questionnaire that focused on pad use, changing underclothes, sleep quality, worn out/tired feelings, work/activities outside the home, depressed feelings and relationship with partner (Table S1).

Statistical analysis

The proportion of patients reporting a positive response (rating their condition as "greatly improved" or "improved") on the TBS were evaluated in the overall pooled population by treatment, and in subgroups of patients by CIC (use/non-use) and UTI status (presence/absence) using the Cochran–Mantel–Haenszel χ^2 method with the dichotomized number of baseline UUI episodes (≤9 or >9) as a stratification factor. The proportion of patients who improved on the KHQ severity measures and specific items at week 12 after treatment was assessed in the overall pooled population using the same Cochran–Mantel–Haenszel method as for the TBS analysis.

Changes from baseline in I-QOL total summary score, I-QOL subscale scores and KHQ domain scores were assessed in the overall pooled population using an ANCOVA model, with treatment group as the factor, and baseline scores, baseline UUI episodes (≤9 or >9) and site as covariates. As the subgroup analyses by CIC use/non-use and UTI status (presence/absence) were post-hoc and the sample sizes were small, statistical comparisons between these groups are not reported.

Results

Baseline demographics and disease characteristics

The overall pooled population comprised 1105 patients randomized to onabotA 100U (n = 557) or placebo (n = 548). Baseline demographics and disease characteristics were balanced between the treatment groups (Table 1). The mean age was 60.4 years; 87.8% were female, mean duration of OAB was 6.1 years and patients reported a mean of 5.4 UI episodes/day. The patients' I-QOL total and subscale scores at baseline ranged from 24.4 to 42.9, whereas KHQ domain scores ranged from 31.3 to 83.4 (Table 1).

Outcome measures

As previously published, treatment with onabotA 100U resulted in significant improvements in patients' OAB symptoms compared with the placebo, with reductions from baseline at week 12 in mean daily episodes of UI (−2.80 *vs* −0.95), urgency (−3.30 *vs* −1.23), micturition (−2.35 *vs*

Table 1 Baseline demographics and disease characteristics (overall pooled population)

Characteristic	Placebo (n = 548)	OnabotA 100U (n = 557)
Age (years)	60.1 ± 13.6	60.6 ± 14.2
Female sex, n (%)	474 (86.5)	496 (89.0)
Duration of OAB (years)	6.1 ± 7.1	6.0 ± 7.1
Prior anticholinergic use	2.5 ± 1.5	2.4 ± 1.5
UI episodes/day	5.4 ± 3.6	5.5 ± 3.7
Urgency episodes/day	8.3 ± 4.1	8.8 ± 4.7
Micturition episodes/day	11.5 ± 3.4	12.0 ± 4.1
Nocturia episodes/day	2.0 ± 1.4	2.2 ± 1.5
I-QOL scores		
Total summary	34.7 ± 18.5	34.1 ± 19.0
Avoidance and Limiting Behavior	31.6 ± 16.9	31.2 ± 17.1
Psychosocial Impact	42.9 ± 23.8	42.3 ± 24.8
Social Embarrassment	25.0 ± 21.1	24.4 ± 20.8
KHQ multi-item domain scores		
Role Limitations	61.2 ± 29.0	65.4 ± 29.0
Social Limitations	42.4 ± 30.6	44.8 ± 31.3
Physical Limitations	64.9 ± 29.9	67.0 ± 28.5
Personal Relationship	36.2 ± 35.9	37.9 ± 35.5
Emotions	55.3 ± 29.3	56.0 ± 31.3
Sleep/Energy	65.3 ± 26.6	64.7 ± 27.0
Severity/Coping	64.6 ± 23.1	65.7 ± 22.8
KHQ single-item domain scores		
General Health Perception	32.2 ± 23.9	31.3 ± 23.8
Incontinence Impact	83.4 ± 23.1	83.3 ± 24.7

Data are mean ± SD unless otherwise indicated.

−0.87) and nocturia (−0.49 *vs* −0.24; $P < 0.001$ *vs* placebo for all parameters).[15,16] Significantly higher proportions of onabotA- than placebo-treated patients achieved a 100% reduction in UI episodes (i.e. became "dry"; 27.1% *vs* 8.4%; $P < 0.001$).[22]

Overall pooled population

A significantly higher proportion of onabotA-treated patients reported a positive response on the TBS compared with placebo (61.8% *vs* 28.0%; $P < 0.001$; Fig. 1). Significantly greater improvements in patients' HRQOL scores were observed after treatment with onabotA compared with placebo (I-QOL total: 22.5 *vs* 6.6; Avoidance and Limiting Behavior: 23.7 *vs* 6.6; Psychosocial Impact: 20.5 *vs* 6.3; Social Embarrassment: 23.8 *vs* 6.8; $P < 0.001$ *vs* placebo for all; Fig. 2a). Improvements in I-QOL total and all subscale scores with onabotA treatment were three to four times those with placebo, and two times the MID, whereas none of the improvements observed with placebo exceeded MID (Fig. 2a).

Improvements from baseline in KHQ Role and Social Limitations domain scores were also significantly greater with onabotA compared with placebo (Role Limitations: −25.4 *vs* −3.7; Social Limitations: −16.8 *vs* −2.5; $P < 0.001$ *vs* placebo for both; Fig. 3a). The same trend was observed for all other KHQ domain scores, with magnitudes of improvement with onabotA ranging from three to seven times the placebo and two to five times the MID, apart from General Health (Fig. 3a).

The negative impact and bother of urinary symptoms on patients' daily lives was significantly reduced at week 12 after treatment with onabotA compared with placebo (Fig. 4). Compared with responses at baseline, a significantly higher proportion of onabotA-treated patients versus placebo reported a decrease in the frequency of pad use (37.6% *vs* 15.3%) and changing underclothes (54.9% *vs* 25.7%) at week 12 ($P < 0.001$ *vs* placebo for both; Fig. 4). Significant improvements were also observed with onabotA versus placebo in other KHQ individual items, including sleep, tired/worn out feelings, work life/daily activities, depressed feelings due to bladder problems and relationship with partner ($P < 0.001$ *vs* placebo for all; Fig. 4).

Subgroups by CIC (use/non-use) and UTI status (presence/absence)

During the first 12 weeks (placebo-controlled period), CIC for urinary retention was initiated in 31 of 557 patients (5.6%) in the onabotA group compared with one of 548 patients (0.2%) in the placebo group. CIC was performed at an average frequency of 2.3 times/day with a median duration of 8.3 weeks in the onabotA group, and 4.7 times/day with a median duration of 2.6 weeks in the placebo group. During the first 12 weeks of treatment, UTI occurred in 99 of 557 patients (17.8%) in the onabotA group and in 30 of 548

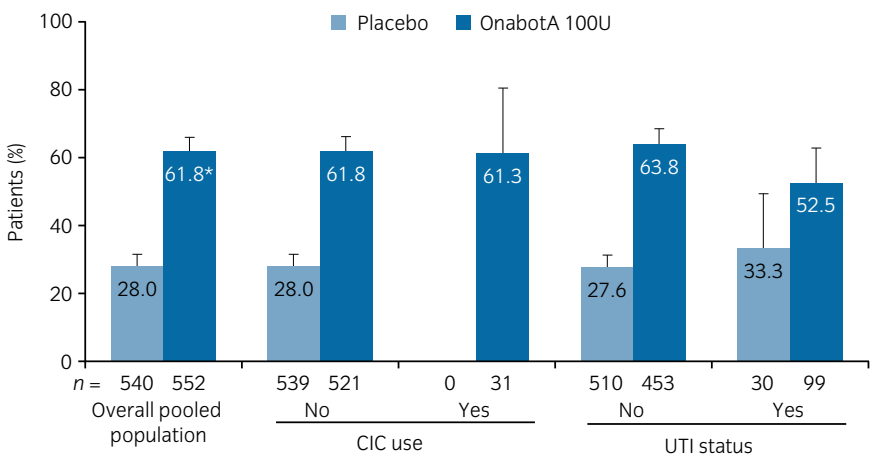
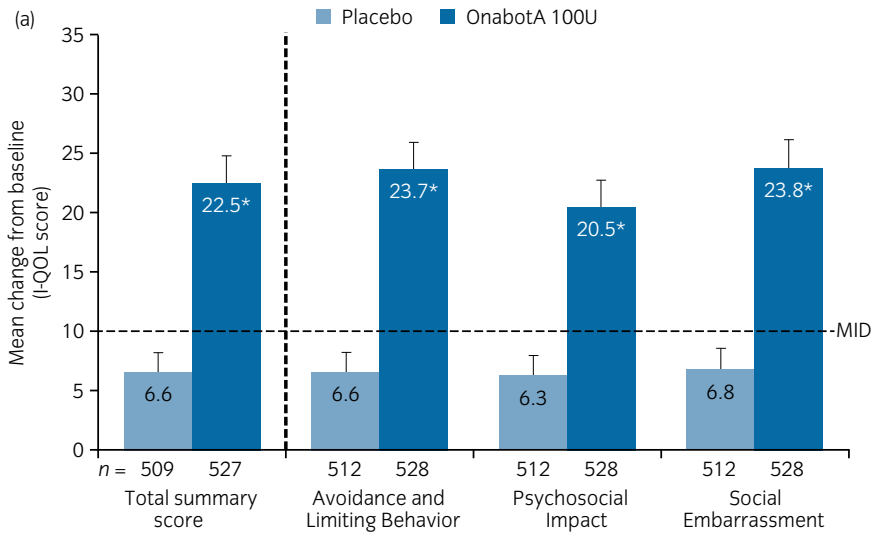
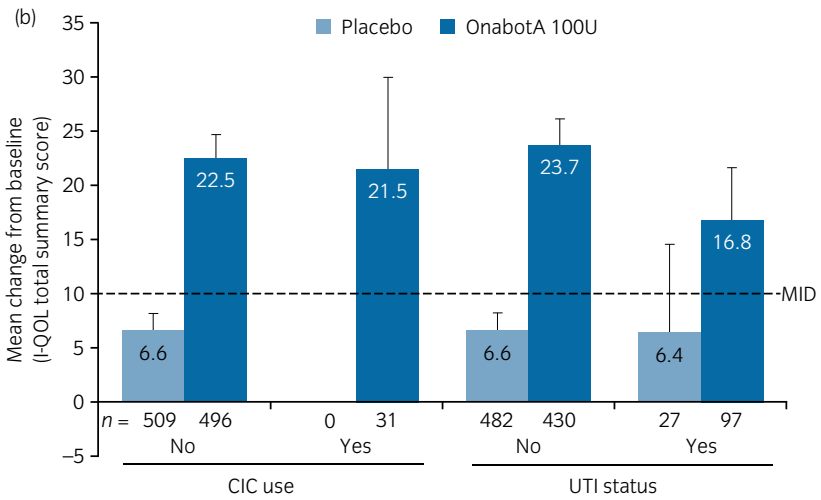


Fig. 1 Proportion of patients with a positive response (their condition "greatly improved" or "improved") on the TBS in the overall pooled population and subgroups by CIC use and UTI status. *$P < 0.001$ versus placebo. Error bars represent 95% confidence intervals. The n values denote the number of patients with data available at week 12.



Baseline I-QOL total summary score: 34.7 (placebo), 34.1 (onabotA)



Baseline I-QOL total summary score (placebo, onabotA)
CIC No: 34.8, 34.1; CIC Yes: 28.4, 34.2
UTI No: 35.2, 34.7; UTI Yes: 26.4, 31.5

Fig. 2 Change from baseline in (a) I-QOL total summary and three subscale scores in the overall pooled population, and (b) I-QOL total summary score in the subgroups by CIC use and UTI status. *$P < 0.001$ versus placebo. Error bars represent 95% confidence intervals. The *n* values denote the number of patients with data available at week 12.

patients (5.5%) in the placebo group, with a median time to onset of 4.7 and 6.2 weeks, respectively.

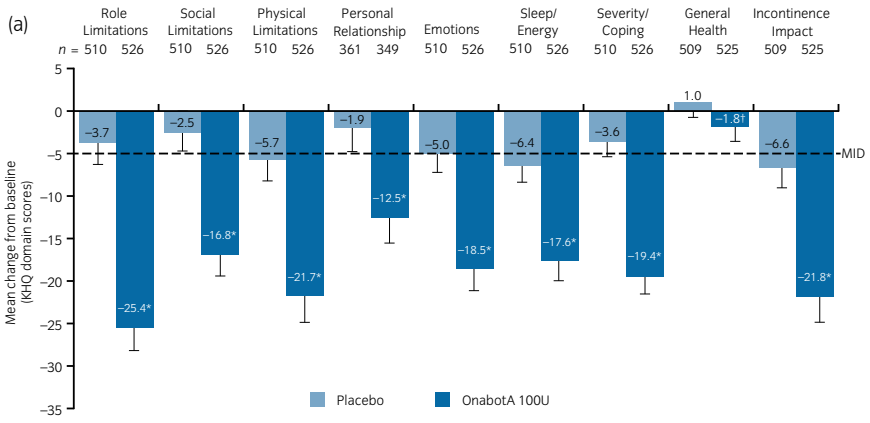
The proportion of patients with a positive TBS response with onabotA treatment was 61.8% in the overall population, and was similar among onabotA-treated patients with or without CIC use (61.3% and 61.8%, respectively; Fig. 1). Although TBS response was slightly lower in onabotA-treated patients with UTI (52.5%) versus those without (63.8%), it was consistently greater for the onabotA group compared with placebo, regardless of UTI status (Fig. 1).

Improvements in I-QOL total score with onabotA were two times the MID, and similar in magnitude in the overall pooled population (22.5), the group with CIC use (21.5) and the group without (22.5; Fig. 2). Slightly smaller improvements in I-QOL total score were noted in onabotA-treated patients with UTI compared with those without UTI (16.8 *vs* 23.7); however, regardless of UTI status, markedly larger improvements (two times the MID) were noted with onabotA treatment compared with placebo (Fig. 2b).

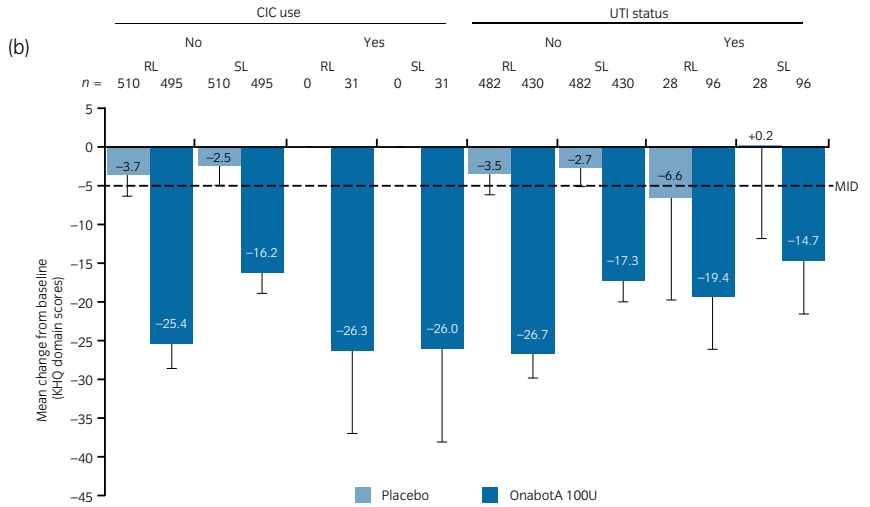
Improvements from baseline were up to five times the MID in the prespecified KHQ domains of Role Limitations and Social Limitations (Fig. 3b), and in all other domains except General Health (Table 2), regardless of CIC use. There was a trend for smaller improvements in all KHQ domain scores in onabotA-treated patients with UTI compared with those without UTI; however, the improvements were two to five times the MID across all the domains except General Health (Fig. 3b; Table 2) in both groups.

Discussion

Given the high burden of symptom bother in patients with OAB who are untreated,[6–8] and the high discontinuation rates with anticholinergic therapies,[11–14] it is important to evaluate



Baseline KHQ domain scores (placebo, onabotA)
RL: 61.2, 65.4; SL: 42.4, 44.8; PL: 64.9, 67.0; PR: 36.2, 37.9; EM: 55.3, 56.0; SE: 65.3, 64.7; SC: 64.6, 65.7; GH: 32.2, 31.3; Incont Impact: 83.4, 83.3



Baseline KHQ domain scores (placebo, onabotA)
CIC No, RL: 61.2, 65.1; SL: 42.3, 44.4. CIC Yes, RL: 66.7, 69.4; SL: 77.8, 52.0
UTI No, RL: 60.5, 64.6; SL: 42.1, 43.7; UTI Yes, RL: 73.9, 68.9; SL: 47.6, 49.9

Fig. 3 Change from baseline in (a) KHQ multi- and single-item domain scores in the overall pooled population, and (b) KHQ Role Limitations and Social Limitations domain scores in the subgroups. *$P < 0.001$; †$P < 0.01$ versus placebo. Error bars represent 95% confidence intervals. The *n* values denote the number of patients with data available at week 12. PR, Personal Relationship; PL, Physical Limitations; RL, Role Limitations; SC, Severity/Coping; SE, Sleep/Energy; SL, Social Limitations.

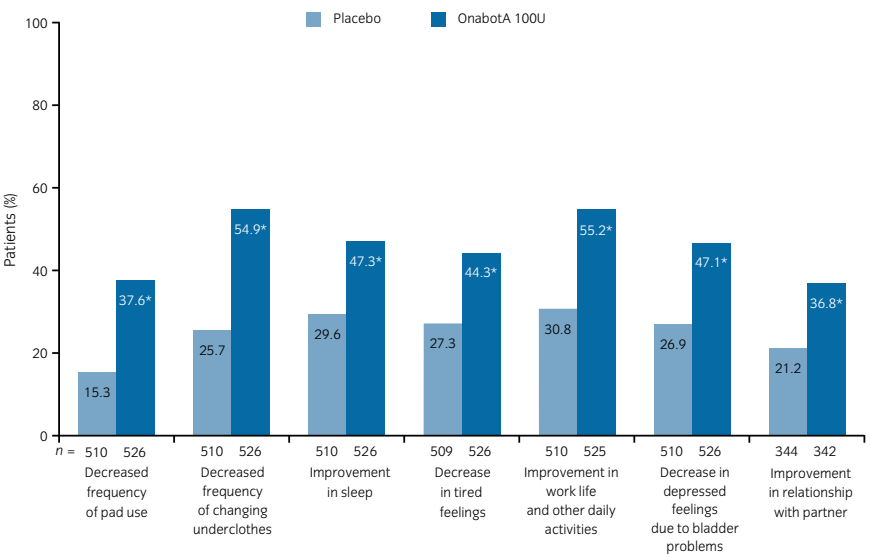


Fig. 4 Proportion of patients with improvements in practical aspects of patients' daily lives at week 12 post-treatment in overall pooled population. *$P < 0.001$ versus placebo. The *n* values denote the number of patients with data available at week 12.

the impact of OAB treatments on patients' lives. This pooled analysis of two large, randomized, phase 3, placebo-controlled studies shows that the OAB symptom improvement previously shown with onabotA 100U is accompanied by a practical benefit on patients' daily lives, with significant improvements across multiple patient-reported outcomes.

Table 2 Change from baseline in KHQ multi-item and single-item domain scores in the subgroups by CIC use and UTI status at week 12 post-treatment (post-hoc analysis)

	CIC use in the first 12 weeks†				UTI‡ status in the first 12 weeks			
	No		Yes		No		Yes	
	Placebo (n = 547)	OnabotA (n = 526)	Placebo (n = 1)	OnabotA (n = 31)	Placebo (n = 518)	OnabotA (n = 458)	Placebo (n = 30)	OnabotA (n = 99)
KHQ multi-item domain scores, mean change from baseline (95% CI)								
Physical Limitations	−5.7 (−8.1, −3.2)	−21.7 (−24.8, −18.6)	0	−21.0 (−30.6, −11.4)	−5.2 (−7.7, −2.7)	−23.3 (−26.6, −19.9)	−13.1 (−23.1, −3.1)	−14.6 (−21.0, −8.2)
Personal Relationship	−1.9 (−4.8, 0.9)	−12.8 (−15.8, −9.8)	0	−6.5 (−19.6, 6.6)	−2.4 (−5.3, 0.4)	−13.0 (−16.3, −9.7)	11.5 (−5.6, 28.7)	−10.1 (−16.1, −4.2)
Emotions	−5.0 (−7.2, −2.9)	−18.7 (−21.3, −16.1)	0	−16.1 (−25.6, −6.7)	−5.0 (−7.2, −2.8)	−19.5 (−22.3, −16.7)	−5.9 (−16.3, 4.4)	−14.1 (−19.7, −8.6)
Sleep/Energy	−6.4 (−8.3, −4.5)	−17.2 (−19.6, −14.8)	0	−24.2 (−34.9, −13.5)	−6.3 (−8.2, −4.3)	−17.7 (−20.3, −15.1)	−8.9 (−18.0, 0.1)	−17.2 (−23.0, −11.3)
Severity/Coping	−3.6 (−5.2, −1.9)	−19.3 (−21.6, −17.1)	0	−20.0 (−29.2, −10.9)	−3.6 (−5.3, −1.9)	−20.1 (−22.5, −17.7)	−2.8 (−10.3, 4.6)	−16.1 (−20.7, −11.5)
KHQ single-item domain scores, mean change from baseline (95% CI)								
General Health Perception	1.0 (−0.6, 2.6)	−2.1 (−4.0, −0.3)	0	3.2 (−3.4, 9.8)	1.1 (−0.5, 2.7)	−2.5 (−4.5, −0.5)	0 (−8.8, 8.8)	1.3 (−2.8, 5.4)
Incontinence Impact	−6.6 (−8.9, −4.3)	−21.7 (−24.8, −18.7)	0	−22.6 (−33.7, −11.5)	−6.6 (−8.9, −4.2)	−22.8 (−26.1, −19.5)	−7.1 (−16.0, 1.7)	−17.4 (−23.8, −10.9)

†CIC was initiated for urinary retention if the post-void residual was ≥200 and <350 mL, and if there were associated symptoms that were deemed to require CIC, or if post-void residual was ≥350 mL, regardless of symptoms. ‡UTI was defined as a positive urine culture with a bacteriuria count of $>10^5$ colony forming units/mL and leukocyturia (>5 per high power field), regardless of symptoms.

Significantly greater improvements were seen with onabotA than placebo in the perception of treatment benefit, and in all I-QOL and disease-specific KHQ domains. Notably, these improvements were clinically meaningful regardless of the use of CIC or the presence of UTI.

Previous studies have shown that, compared with the general population, patients with OAB have higher rates of dissatisfaction with their sleep quality, work life and sexual function, and express greater feelings of depression and stress.[7,8] Our analysis found that treatment with onabotA significantly improved sleep quality, relationship with partner and work life/daily activities. Patients also reported a significant decrease in depressed and tired feelings as a result of bladder problems, as well as a significant decrease in how often they had to use pads and change their underclothes after treatment with onabotA. To our knowledge, this is the first randomized, placebo-controlled, pooled study to show the efficacy of onabotA across the specific questions in the KHQ that address these practical aspects of daily living.

Few studies have evaluated the impact of CIC on HRQOL outcomes in OAB patients. Similar to Khan *et al.*,[23] results from our post-hoc analyses show that CIC use did not diminish the HRQOL improvements with onabotA. A potential explanation for this finding is that, among the minority of patients who initiated CIC (5.6% overall), it was performed only an average of 2.3 times/day and thus, the demands of CIC might seem small to patients compared with the benefit gained from treatment with onabotA. In addition, a previous study showed that once patients learn and adhere to the technique of CIC, they actually report improvements in their HRQOL scores, possibly because of the additional control over OAB symptoms that CIC provides.[24]

The post-hoc analyses in the subgroup by UTI status showed that UTI somewhat reduced the magnitude of improvement in HRQOL scores in onabotA-treated patients with UTI; however, regardless of UTI status, the improvements were clinically relevant (two to five times the MID) across all but the General Health domains. The marked improvements observed in HRQOL despite UTI might be explained by the fact that UTI is a transient event. Previously published analyses in this subgroup of patients showed that regardless of the presence or absence of UTI, onabotA reduced the daily episodes of UI compared with placebo.[25]

One limitation of the present analysis was that the HRQOL assessments in the subgroups were post-hoc, and the sample sizes of the subgroups were small, hence the results should be interpreted accordingly. In addition, the HRQOL outcomes were evaluated by patient-reported questionnaires, and thus were subjective in nature. Nevertheless, patient-reported measures are valuable tools used to capture patient perspectives, and are recognized as an important component in the assessment of OAB treatment efficacy.

In this pooled analysis of OAB patients with UI who were inadequately managed by ≥1 anticholinergic, the majority of patients reported treatment benefit after onabotA 100U therapy. Significant improvements were demonstrated across individual and overall HRQOL outcomes. Notably, these results were observed regardless of the need for CIC or the occurrence of UTI. The results of this study suggest that onabotA is

an effective treatment in OAB patients with UI, and provides clinically meaningful improvements in patients' daily lives.

Acknowledgments

Assistance with the writing and development of the manuscript was provided by Jaya Kolipaka of Evidence Scientific Solutions, and was funded by Allergan, Inc. All authors were involved in data analysis and interpretation, drafting of the manuscript and critical revision of the manuscript for important intellectual content. All authors provided final approval to submit the manuscript. The authors acknowledge all the participating investigators in the individual phase 3 studies.[15,16]

Conflict of interest

This study was funded by Allergan, Inc. Data were collected by the investigators at the study centers, and were monitored and analyzed by Allergan, Inc. Dr Everaert is a consultant and lecturer for Allergan, Inc., and has received honoraria, and educational and travel grants from Allergan, Inc. Dr Gruenenfelder is a consultant and trial investigator for Allergan, Inc. Dr Schulte-Baukloh is a consultant and trial investigator for Allergan, Inc. Dr Egerdie is a coordinating investigator for Allergan, Inc., and Eli Lilly; is an advisory board participant and a speaker for Allergan, Inc., Abbott, Amgen, Astellas, Bayer HealthCare, Eli Lilly, GlaxoSmithKline and Pfizer; is a speaker for AstraZeneca; is an advisory board participant and consultant for Spectrum; and is a consultant for Amgen, Astellas, Eli Lilly and Protox Therapeutics. Dr Khalaf was an employee of Allergan, Inc. at the time of the study. She is presently at Xcenda. Dr Joshi and Dr Ni are employees of Allergan, Inc. Dr Sussman is a consultant and trial investigator for Allergan, Inc.; is a consultant for AMS and Medtronic; and is a meeting participant/lecturer for Astellas and Actavis.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1 KHQ individual items.

