

ONABOTULINUMTOXINA SIGNIFICANTLY IMPROVES URINARY INCONTINENCE AND QUALITY OF LIFE IN OVERACTIVE BLADDER PATIENTS REGARDLESS OF INCONTINENCE SEVERITY AT BASELINE

Hypothesis / aims of study

The symptoms of overactive bladder (OAB), particularly incontinence, have a profound negative impact on patients' quality of life (QOL). OnabotulinumtoxinA 100U has been shown to reduce urinary incontinence (UI) and improve QOL in two phase 3, randomized, placebo-controlled trials of patients with OAB who were inadequately managed by ≥ 1 anticholinergic. In order to determine whether severity of incontinence at baseline can influence response to onabotulinumtoxinA in patients with OAB, this post hoc analysis evaluated the effect of onabotulinumtoxinA 100U on UI and QOL according to the severity of incontinence at baseline.

Study design, materials and methods

Two phase 3 trials (NCT0091845 and NCT00910520), which were identical in design, enrolled OAB patients (N=1105) who had experienced ≥ 3 urgency UI episodes over a 3-day period and ≥ 8 micturitions per day. All patients were inadequately managed by ≥ 1 anticholinergic. Patients with stress predominant UI were excluded. Patients were randomized 1:1 to receive onabotulinumtoxinA 100U (n=557) or placebo (n=548), via cystoscopic intradetrusor injections (20 at 0.5 mL/injection), sparing the trigone. Data from these phase 3 trials were pooled for analysis and grouped by severity of UI at baseline: ≤ 2 (n=188), > 2 to ≤ 5 (n=435), and > 5 (n=482) UI episodes/day. Efficacy and safety assessments at week 12, following a single treatment, included change and percent change from baseline in UI episodes/day, proportion of patients with $\geq 50\%$ and 100% reduction in UI episodes, change from baseline in Incontinence-Quality of life (I-QOL) total score, and adverse events. Increases from baseline indicate improvement on the I-QOL questionnaire, for which the minimally important difference (MID) was based on published literature and determined *a priori* to be +10 points. Efficacy analyses were conducted using the overall pooled intent-to-treat population (all randomized patients). Adverse events were evaluated in the safety population, which comprised all patients who received any treatment.

Results

The baseline mean UI episodes/day in the onabotulinumtoxinA and placebo groups were 1.5, 3.6, and 8.9; and 1.5, 3.6, and 8.5 in the ≤ 2 , > 2 to ≤ 5 , and > 5 UI subgroups, respectively. Baseline characteristics were similar across the subgroups, with one exception: the proportion of patients ≥ 75 years old was higher in the subgroup with > 5 UI episodes at baseline (21.3% and 18.6% in onabotulinumtoxinA and placebo groups, respectively) compared with those in the ≤ 2 (11.1% and 11.2%) and > 2 to ≤ 5 UI (11.9% and 11.1%) subgroups. For the ≤ 2 , > 2 to ≤ 5 , and > 5 baseline UI subgroups, onabotulinumtoxinA resulted in significantly greater reductions in UI versus placebo (-0.7 vs +0.1, -1.9 vs -0.7, and -4.5 vs -1.5 episodes/day; $P < 0.0001$ for all). Although mean reduction in UI episodes/day with onabotulinumtoxinA increased with increasing baseline UI severity, the percent reduction in UI was similar (range: 43.8% to 52.1%) for all subgroups, regardless of UI severity. A consistently higher proportion of onabotulinumtoxinA than placebo patients achieved $\geq 50\%$ UI reduction (56.6 vs 33.7%; 66.5 vs 34.1%; and 56.7 vs 27.3% in the ≤ 2 , > 2 to ≤ 5 , and > 5 UI subgroups) and 100% UI reduction (41.4 vs 20.2%; 31.2 vs 9.2%; and 17.5 vs 3.3% in the ≤ 2 , > 2 to ≤ 5 , and > 5 UI subgroups). The proportion of patients who became dry (i.e., 100% UI reduction) was greatest among onabotulinumtoxinA-treated patients with ≤ 2 UI episodes at baseline and decreased with increasing UI severity. The likelihood of being dry following onabotulinumtoxinA vs placebo was greatest for the most severe UI patients and decreased with decreasing UI severity (odds ratio [95% CI] = 2.8 [1.5–5.4]; 4.5 [2.6–7.7]; and 6.2 [2.8–13.5] in the ≤ 2 , > 2 to ≤ 5 , and > 5 UI subgroups). Improvements in I-QOL total score with onabotulinumtoxinA were consistently 1.5 to 2 times the MID and significantly greater than placebo in all subgroups (19.4 vs 7.8 for ≤ 2 ; 24.4 vs 6.6 for > 2 to ≤ 5 ; and 22.0 vs 6.1 for > 5 UI subgroups; $P < 0.0001$ for all). The most common adverse events were urinary tract infection (UTI) and dysuria. UTI occurred with increased frequency in both onabotulinumtoxinA- and placebo-treated patients in the > 5 UI subgroup (25.1% and 10.0%), compared with the ≤ 2 (11.2% and 2.3%) and > 2 to ≤ 5 (13.0% and 1.9%) UI subgroups. The incidence of dysuria with onabotulinumtoxinA versus placebo was 12.2% vs 12.6%, 8.3% vs 5.6%, and 8.4% vs 5.4% in the ≤ 2 , > 2 to ≤ 5 , and > 5 baseline UI subgroups, respectively.

Interpretation of results

The results of this post hoc analysis of the pooled phase 3 clinical trials demonstrate that patients treated with onabotulinumtoxinA experienced significantly greater reductions in UI episodes compared with placebo, regardless of baseline severity. Patients with the most severe incontinence at baseline (> 5 UI episodes/day) had similar percent reductions in UI and improvements in QOL as those with less severe incontinence (≤ 2 UI episodes/day) following treatment with onabotulinumtoxinA. As might be expected, the proportion of onabotulinumtoxinA-treated patients achieving complete continence (i.e., 100% reduction in UI episodes) at week 12 was higher in the subgroup with less severe incontinence at baseline. Interestingly, the odds of becoming continent versus placebo were highest for those with the most severe incontinence at baseline. Patients with the most severe incontinence were older, and experienced more UTIs with both placebo and onabotulinumtoxinA treatment relative to those with less severe incontinence.

Concluding message

Irrespective of incontinence severity at baseline, onabotulinumtoxinA provides significantly greater improvements in UI and QOL, compared with placebo, in patients with OAB who were inadequately managed by ≥ 1 anticholinergic. The overall percent reduction in incontinence episodes was similar, irrespective of baseline incontinence severity; however, patients with less incontinence at baseline were more likely to be dry. The subgroup with >5 UI episodes tended to be older and experienced more UTIs with both placebo and onabotulinumtoxinA treatment; all other baseline characteristics and adverse events were similar between the subgroups.

Disclosures

Funding: Allergan, Inc. **Clinical Trial:** Yes **Registration Number:** NCT00910845 and NCT00910520 **RCT:** Yes **Subjects:** HUMAN **Ethics Committee:** Institutional Review Board (IRB) **Helsinki:** Yes **Informed Consent:** Yes