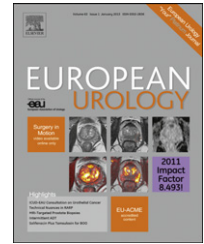


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Platinum Priority – Benign Prostatic Hyperplasia
Editorial by Prokar Dasgupta on pp. 504–505 of this issue

A Randomized Double-blind Placebo-controlled Phase 2 Dose-ranging Study of OnabotulinumtoxinA in Men with Benign Prostatic Hyperplasia

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Abstract

Background: Botulinum toxin treatment has been investigated as a minimally invasive alternative to oral medications in men with lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (LUTS/BPH).

Objective: To explore the efficacy of onabotulinumtoxinA 100 U, 200 U, and 300 U versus placebo in men with LUTS/BPH in a phase 2 dose-ranging study.

Design, setting, and participants: A multicenter double-blind randomized, placebo-controlled 72-wk study enrolled men ≥ 50 yr of age with LUTS/BPH, International Prostate Symptom Score (IPSS) ≥ 12 , total prostate volume (TPV) 30–100 ml, and maximum flow rate (Q_{max}) 5–15 ml/s.

Intervention: Single transperineal ($n = 63$) or transrectal ($n = 311$) administration of placebo ($n = 94$) or onabotulinumtoxinA 100 U ($n = 95$), 200 U ($n = 94$), or 300 U ($n = 97$) into the prostate transition zone.

Outcome measurements and statistical analysis: The primary efficacy end point was a change from baseline in IPSS at week 12. Secondary end points were Q_{max} , TPV, and transition zone volume (TZV). Analysis of covariance and the Cochran-Mantel-Haenszel method assessed the efficacy and proportion of IPSS responders. Adverse events (AEs) were assessed.

Results and limitations: Significant improvements from baseline in IPSS, Q_{max} , TPV, and TZV were observed for all groups, including placebo, at week 12 ($p < 0.001$), with no significant differences between onabotulinumtoxinA and placebo. However, in an exploratory post hoc analysis, a significant reduction in IPSS versus placebo was observed with onabotulinumtoxinA 200 U in prior α -blocker users ($n = 180$) at week 12. AEs were comparable across all groups.

Conclusions: Reductions in LUTS/BPH symptoms were seen in all groups, including placebo, with no significant between-group differences owing to a large placebo effect from the injectable therapy. The findings from the post hoc analysis in men previously treated with α -blockers will be further explored in an appropriately designed study.

Trial registration: <http://www.ClinicalTrials.gov>; NCT00284518.

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1. Introduction

Lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH; LUTS/BPH) is one of the most prevalent disorders in aging men, resulting in a significant burden on patients' general quality of life (QoL) [1]. Because commonly used oral medications such as α -blockers and 5 α -reductase inhibitors (5-ARIs) have limitations, including the requirement for daily dosing, many patients switch or discontinue therapy because of the loss of efficacy over time or side effects [2]. The use of botulinum toxins for the treatment of LUTS/BPH has been explored as a minimally invasive alternative in those men not responding to oral therapies and/or who do not want surgery; however, almost all trials investigating the use of botulinum toxins in LUTS/BPH were small [3–9], and only one 30-patient study was placebo controlled [3].

The objective of this phase 2 study was to evaluate the efficacy of a range of onabotulinumtoxinA doses (100 U, 200 U, and 300 U) administered to the prostate compared with placebo treatment in reducing the International Prostate Symptom Score (IPSS) in men with moderate or severe LUTS/BPH. Safety and supplementary efficacy outcomes were also evaluated.

2. Patients and methods

2.1. Study participants

Men ≥ 50 yr of age with LUTS presumably due to BPH for ≥ 3 mo based on medical history and digital rectal examination (DRE) were screened to determine their eligibility for the study. In addition to patient age and duration of LUTS, inclusion criteria included weight of at least 50 kg, an IPSS ≥ 12 , total prostate volume (TPV) 30–100 ml, maximum flow rate (Q_{max}) 5–15 ml/s, and a postvoid residual (PVR) urine volume < 200 ml at the screening visit. Patients who had not used oral BPH medications were eligible for inclusion. Patients on BPH medications at screening required a washout of 15 d for α -blockers, 30 d for phytotherapy drugs used for prostate or urinary symptoms, or 90 d for 5-ARIs; these medications were prohibited for the duration of the study. Patients were excluded if they had previous prostate surgery including minimally invasive procedures, prostate-specific antigen (PSA) level ≥ 10 μ g/l, a history of prostatitis, prostate or bladder cancer, bladder surgery, recurrent urinary tract infections, acute urinary retention or use of an indwelling catheter within 3 mo of screening, or previous use of any serotype of botulinum therapy for a urologic condition. For nonurologic conditions, botulinum toxins were permitted > 3 mo prior to randomization.

2.2. Study design

This was a phase 2 double-blind placebo-controlled, prospective, randomized 72-wk dose-ranging study conducted at 50 centers in Europe, Asia-Pacific, and North America (<http://www.clinicaltrials.gov>; NCT00284518). The study complied with the principles of the Declaration of Helsinki and was approved by the institutional review boards/independent ethics committees at participating centers. All patients provided written informed consent.

Patients were randomized 1:1:1:1 via an interactive voice- or Web-response system to receive placebo, consisting of 0.9% sterile saline, or onabotulinumtoxinA (Botox, Allergan, Inc., Irvine, CA, USA) 100 U, 200 U,

or 300 U. [Authors' note: Units of biologic activity of onabotulinumtoxinA cannot be compared with or converted into units of any other botulinum toxin product, and onabotulinumtoxinA is not interchangeable with other botulinum toxins.] Randomization was stratified by TPV (< 40 ml and ≥ 40 ml) at baseline and within each study site. Study drug was administered as an outpatient procedure under transrectal ultrasound guidance at three locations (cranial, middle, and caudal) within the transition zone of each lateral prostate lobe via the transperineal route and then, after a protocol amendment, the transrectal route (Fig. 1). The route of administration was changed from transperineal to transrectal after only 63 patients were enrolled because transrectal administration is more familiar to urologists who perform similar procedures (eg, transrectal biopsies of the prostate). Patients received prophylactic antibiotics (ciprofloxacin 500 mg twice daily or levofloxacin 500 mg once daily) 2 h before administration of the study medication and for a minimum of 3 d posttreatment. No anesthesia, local anesthesia, injection, or sedation was used according to local site practice. The total injection volume (which depended on the size of the prostate gland) was up to approximately 20% of TPV for the first 23 patients enrolled but was changed to a maximum of about 12% of TPV following a protocol amendment (4- to 9-ml injection volume).

2.3. Efficacy and safety evaluations

Patients were evaluated at weeks 2, 4, 8, and 12 following treatment, and every 8 wk thereafter until exit at week 72. IPSS, vital signs, urinalysis, Q_{max} , PVR, and adverse events (AEs) were evaluated at each visit. Transrectal prostate volume assessment as well as bladder and kidney ultrasounds were done at screening and at weeks 12, 28, 52, and 72 (or exit). The primary efficacy end point was the change from baseline in IPSS at week 12. Secondary efficacy end points included IPSS responder analysis (patients with a ≥ 4 -point decrease from baseline in total IPSS), changes from baseline in Q_{max} , TPV, and transition zone volumes (TZVs), and PVR at week 12. In addition, sexual function was assessed using the International Index of Erectile Function (IIEF) [10] at screening and at weeks 4, 8, 12, 28, 52, and 72. Safety end points included AEs, vital signs, physical examinations, DRE, laboratory (hematology, chemistry, and urinalysis) evaluations, serum PSA, PVR, and kidney and bladder ultrasound.

2.4. Statistical analysis

A sample size of 350 patients was calculated for this phase 2 study to provide a power of 43–99% to detect a 2- to 5-point change from baseline in total IPSS between the treatment groups, given an estimated standard deviation of 6. Efficacy analyses were conducted using the intent-to-treat (ITT) population (all randomized patients). Within-group changes from baseline were evaluated using paired *t* tests. The primary efficacy end point was evaluated using an analysis of covariance (ANCOVA) main effect model, with baseline and stratification factor (prostate volume) as covariates; missing scores at week 12 were imputed using the last observation carried forward method. The two-sided 95% confidence intervals were constructed for the difference in the least square means between onabotulinumtoxinA and placebo; *p* values ≤ 0.05 were considered statistically significant. QoL was evaluated using item 8 from the IPSS: "If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?" It was scored from 0 (very satisfied) to 6 (very dissatisfied). QoL, Q_{max} , TPV, TZV, PSA, and PVR were analyzed using the same ANCOVA models as the primary efficacy analysis. The proportion of IPSS responders was analyzed using the Cochran-Mantel-Haenszel method. The safety population (all patients who received study treatment) was used for the safety analysis.

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