ORIGINAL ARTICLE

Anticholinergic Therapy vs. OnabotulinumtoxinA for Urgency Urinary Incontinence

Anthony G. Visco, M.D., Linda Brubaker, M.D., Holly E. Richter, Ph.D., M.D., Ingrid Nygaard, M.D., Marie Fidela R. Paraiso, M.D., Shawn A. Menefee, M.D., Joseph Schaffer, M.D., Jerry Lowder, M.D., Salil Khandwala, M.D., Larry Sirls, M.D., Cathie Spino, D.Sc., Tracy L. Nolen, Dr.P.H., Dennis Wallace, Ph.D., and Susan F. Meikle, M.D., M.S.P.H., for the Pelvic Floor Disorders Network

ABSTRACT

BACKGROUND

Anticholinergic medications and onabotulinumtoxinA are used to treat urgency urinary incontinence, but data directly comparing the two types of therapy are needed.

METHODS

We performed a double-blind, double-placebo–controlled, randomized trial involving women with idiopathic urgency urinary incontinence who had five or more episodes of urgency urinary incontinence per 3-day period, as recorded in a diary. For a 6-month period, participants were randomly assigned to daily oral anticholinergic medication (solifenacin, 5 mg initially, with possible escalation to 10 mg and, if necessary, subsequent switch to trospium XR, 60 mg) plus one intradetrusor injection of saline or one intradetrusor injection of 100 U of onabotulinumtoxinA plus daily oral placebo. The primary outcome was the reduction from baseline in mean episodes of urgency urinary incontinence per day over the 6-month period, as recorded in 3-day diaries submitted monthly. Secondary outcomes included complete resolution of urgency urinary incontinence, quality of life, use of catheters, and adverse events.

RESULTS

Of 249 women who underwent randomization, 247 were treated, and 241 had data available for the primary outcome analyses. The mean reduction in episodes of urgency urinary incontinence per day over the course of 6 months, from a baseline average of 5.0 per day, was 3.4 in the anticholinergic group and 3.3 in the onabotulinumtoxinA group (P=0.81). Complete resolution of urgency urinary incontinence was reported by 13% and 27% of the women, respectively (P=0.003). Quality of life improved in both groups, without significant between-group differences. The anticholinergic group had a higher rate of dry mouth (46% vs. 31%, P=0.02) but lower rates of catheter use at 2 months (0% vs. 5%, P=0.01) and urinary tract infections (13% vs. 33%, P<0.001).

CONCLUSIONS

Oral anticholinergic therapy and onabotulinumtoxinA by injection were associated with similar reductions in the frequency of daily episodes of urgency urinary incontinence. The group receiving onabotulinumtoxinA was less likely to have dry mouth and more likely to have complete resolution of urgency urinary incontinence but had higher rates of transient urinary retention and urinary tract infections. (Funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Institutes of Health Office of Research on Women's Health; ClinicalTrials.gov number, NCT01166438.)

From the Department of Obstetrics and Gynecology, Duke University Medical Center, Durham (A.G.V.), and RTI International, Research Triangle Park (T.L.N., D.W.) — both in North Carolina; the Departments of Obstetrics and Gynecology and Urology, Stritch School of Medicine, Loyola University, Chicago (L.B.); the Department of Obstetrics and Gynecology, University of Alabama at Birmingham, Birmingham (H.E.R.); the Department of Obstetrics and Gynecology, University of Utah, Salt Lake City (I.N.); the Department of Obstetrics and Gynecology, Cleveland Clinic, Cleveland (M.F.R.P.); the Department of Obstetrics and Gynecology, Kaiser Permanente San Diego, San Diego, CA (S.A.M.); the Department of Obstetrics and Gynecology, University of Texas Southwestern Medical Center, Dallas (J.S.); the University of Pittsburgh, Pittsburgh (J.L.); Oakwood Hospital and Medical Center, Dearborn (S.K.), the Department of Urology, Beaumont Health System, Oakland University William Beaumont School of Medicine, Royal Oak (L.S.), and the Department of Biostatistics, University of Michigan, Ann Arbor (C.S.) — all in Michigan; and the Contraception and Reproductive Health Branch, Center for Population Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Rockville, MD (S.F.M.). Address correspondence to Dr. Visco at the Department of Obstetrics and Gynecology, Duke University Medical Center, 5324 McFarland Dr., Suite 310, Durham, NC 27707, or at anthony.visco@duke.edu.

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Urgency urinary incontinence is characterized by unpredictable loss of urine; it is a prevalent condition that occurs disproportionately in women, affecting up to 19% of older women in the United States.[1] Anticholinergic medications are used as the primary treatment for this condition. A recent systematic review of trials comparing treatments for urgency urinary incontinence showed that none of the six drugs evaluated was superior to another in treating the condition and that current evidence was insufficient to guide the choice among other therapies, including injections of botulinum toxin.[2] OnabotulinumtoxinA is effective in treating urgency urinary incontinence that is resistant to anticholinergic therapy, but this treatment can result in incomplete bladder emptying, necessitating temporary bladder catheterization.[3] Data directly comparing onabotulinumtoxinA with anticholinergic agents have been lacking. We conducted a randomized trial comparing an oral anticholinergic medication regimen with a single injection into the detrusor muscle of onabotulinumtoxinA in women with urgency urinary incontinence to assess the reduction in episodes of urgency urinary incontinence over the course of 6 months, improvement in quality of life, and side effects.

METHODS

STUDY DESIGN

The Anticholinergic versus Botulinum Toxin Comparison (ABC) study was a 10-center, randomized, double-blind, double-placebo–controlled trial involving women without neurologic disease who had moderate-to-severe urgency urinary incontinence; we conducted the trial from February 2, 2010, through May 2, 2012. The study design has been published previously,[4] and the protocol is available with the full text of this article at NEJM.org. Women with five or more episodes of urgency urinary incontinence, as recorded in a 3-day diary, and urgency-predominant urinary incontinence were invited to participate in the trial if they had not previously received anticholinergic drugs or had previously received up to two anticholinergic medications other than solifenacin, darifenacin, or trospium chloride. We excluded women who had a residual urine volume of 150 ml or more after voiding and those who reported previous therapy for urgency urinary incontinence with onabotulinumtoxinA. Women who were receiving anticholinergic therapy at baseline underwent a 3-week washout. Before they underwent randomization, participants had to demonstrate that they or a caregiver could perform bladder catheterization.

Participants were randomly assigned, in a 1:1 ratio, to the oral anticholinergic drug solifenacin, starting at a dose of 5 mg daily, for 6 months (with an initial option of dose escalation of solifenacin and a subsequent option of a switch to trospium XR) plus a single injection into the detrusor muscle of saline or a single injection into the detrusor muscle of 100 U of onabotulinumtoxinA (Botox, Allergan) plus a 6-month oral placebo regimen (Fig. S1 in the Supplementary Appendix, available at NEJM.org). We chose the anticholinergic medications — solifenacin and trospium — with several factors in mind, including mechanisms of action that differed from one another and availability of both drugs in once-daily formulations.[4-6] Randomization was stratified according to previous exposure or no previous exposure to anticholinergic drugs, baseline severity of urgency urinary incontinence (5 to 8 episodes vs. ≥9 episodes of urgency urinary incontinence in a 3-day period), and site.

Participants who were randomly assigned to the anticholinergic group initiated treatment with solifenacin at a dose of 5 mg daily; office visits were scheduled every 2 months. The Patient Global Symptom Control (PGSC) instrument was used to assess whether the current treatment was providing adequate control of urinary leakage; responses to the statement, "This treatment has given me adequate control of my urinary leakage" range from 1 (disagree strongly) to 5 (agree strongly).[7] Dose escalation was allowed at months 2 and 4 if the score on the PGSC was 1 to 3, indicating inadequate symptom control, and if the participant reported that the side effects from the drug were tolerable. With dose escalation at month 2, the dose of solifenacin was increased to 10 mg; if inadequate control of symptoms continued at month 4, the drug was changed to trospium XR at a dose of 60 mg. Participants with PGSC scores higher than 3 continued the regimen they were currently receiving until the next 2-month visit. Participants who were randomly assigned to the onabotulinumtoxinA group were offered dose es-

calation of the placebo on the basis of the same criteria (Fig. S2 in the Supplementary Appendix).

At 6 months, all oral study medications were discontinued. Participants in both groups who had adequate control of symptoms (PGSC score of 4 to 5) and who did not receive off-protocol treatment for urgency urinary incontinence were followed monthly for up to 6 additional months (12 months from randomization) in order to assess the duration of effect.

STUDY OVERSIGHT

The institutional review board at each participating site approved the protocol, and an independent data and safety monitoring board reviewed the progress and safety of the study. No industry support (funding or provision of medications) was received. All participants signed a consent form approved by the local institutional review board. The senior statistician for this study vouches for the accuracy of the reported data and for the fidelity of the study to the protocol.

STUDY OUTCOMES

The primary outcome was the change from baseline in the mean number of episodes of urgency urinary incontinence over the course of 6 months, as reported for 3-day periods in monthly bladder diaries. Secondary efficacy outcomes included the proportion of participants with complete resolution of urgency urinary incontinence and the proportion with more than 75% reduction in urgency urinary incontinence; scores each month on the Overactive Bladder Questionnaire Short Form (OABq-SF)[8,9]; scores at 2, 4, and 6 months on the PGSC; and scores at 3 and 6 months on the following quality-of-life instruments administered during telephone interviews: the Pelvic Floor Distress Inventory Short Form (PFDI-SF),[10] the Pelvic Floor Impact Questionnaire Short Form (PFIQ-SF),[10] and the Patient Global Impression of Improvement (PGI-I).[11] The OABq-SF includes a symptom-severity scale and a quality-of-life scale, each of which ranges from 0 to 100. Higher scores on the symptom-severity scale indicate worse symptoms, whereas higher scores on the quality-of-life scale indicate better quality of life. The PFDI-SF measures the level of distress from pelvic-floor disorders, and the PFIQ-SF measures the effect of pelvic-floor disorders on daily life; scores on both scales range from 0 to 300, with higher values indicating greater distress and greater negative effect on daily life, respectively. The PGI-I is a patient-reported measure of perceived improvement with treatment, on a scale of 1 (very much better) to 7 (very much worse).

At 6 months, oral study drugs, active or placebo, were discontinued. To determine the duration of effect, we contacted the participants by telephone monthly from that point until 12 months after randomization or until they reported inadequate symptom control (PGSC score of 1 to 3).

Outcomes with respect to safety and side effects included any serious adverse event, defined as death, disability, life-threatening illness, or an event requiring hospitalization; the proportion of participants reporting nonserious adverse events that were known to be associated with either treatment, including dry mouth, dry eyes, constipation, and urinary tract infection; and the proportion of patients requiring intermittent catheterization because of residual volume of more than 300 ml after voiding or residual volume of more than 150 ml that was rated by the participant as moderately or quite bothersome. Catheterizations that were performed off-protocol were also recorded.

STATISTICAL ANALYSIS

We estimated that with 121 participants in each treatment group, the study would have 80% or greater power to detect a mean between-group difference in the reduction from baseline of episodes of urgency urinary incontinence of at least 0.8 episodes per day, assuming a standard deviation of 2.1, a two-sided type I error rate of 0.05, and a 10% loss to follow-up over the 6-month study period, and with one interim analysis performed. The interim analysis, which included 191 participants (94 in the onabotulinumtoxinA group and 97 in the anticholinergic group), did not reach the O'Brien–Fleming-type boundaries of the Lan–DeMets alpha spending function (alpha of 0.003), leaving a 0.047 significance level for the end-of-study primary hypothesis test.

For all efficacy analyses, we used a modified intention-to-treat approach, in which data from all participants who underwent randomization and received a study medication and who had a baseline and at least one follow-up measure for the outcome under consideration were analyzed according to the group to which the participants had been assigned. For the primary analysis, missing

data were assumed to be missing at random. The safety analyses were performed on data from all participants who underwent randomization and received a study medication, according to the actual treatment received.

For the primary analyses, we used a linear mixed model with participant-month in the study (1 through 6) as the unit of analysis and the change from baseline in the number of episodes of urgency urinary incontinence as the outcome, with terms for treatment group, month, and the interaction of treatment group with month and categorical covariates of previous or no previous exposure to anticholinergic drugs, baseline severity of urgency urinary incontinence, and site consistent with the randomization stratification variables. Study participant was treated as a random effect to account for the correlation in outcomes over time within a participant. The model generated adjusted estimates of change in the number of episodes of urgency urinary incontinence from baseline for each treatment group and month, and an F-test was used to test the hypothesis that the mean change from baseline across the 6 months differed between the treatment groups. Terms for the interaction of treatment with the stratification factors were added to evaluate whether the treatment effect differed according to these factors.

Similar models were used to evaluate whether continuous measures assessed over time differed between the two treatment groups, with modifications to account for the varied timing of the measurements. For analyses of binary outcome measures assessed over time, we used a robust Poisson regression model, implemented with a generalized linear model assuming Poisson distribution and log link, that had a model structure analogous to that described for the primary analyses, appropriately accounting for the timing of the measurement. Aggregate binary measures of efficacy and safety were evaluated with the use of contingency tables, with differences between treatment groups assessed with the use of Mantel–Haenszel tests that accounted for randomization strata. Differences in the duration of effect between treatment groups were evaluated with the use of Kaplan–Meier product-limit estimates and associated log-rank tests. In the case of any binary outcome with zero events for either group, comparisons were performed with the use of Fisher's exact tests.

Because all analyses other than the primary analysis are considered to be descriptive, no adjustments have been made for multiple testing, and P values should be interpreted accordingly. Analyses were performed with the use of SAS software, version 9.2 (SAS Institute).

RESULTS

PARTICIPANTS

Of the 472 women screened at 10 participating sites (Fig. 1), 249 underwent randomization, 247 received a study medication, and 241 had data available for the primary outcome analyses. The rate of completion of the 6-month active-treatment period was 93% in both groups: 118 participants randomly assigned to anticholinergic medication and 113 assigned to onabotulinumtoxinA completed that phase of the study (P=0.93) (Fig. 1). At baseline, participants reported a mean (±SD) of 5.0±2.7 episodes of urgency urinary incontinence per day, and 41% had not previously received anticholinergic therapy. There were no significant between-group differences with respect to demographic characteristics, baseline severity of urgency urinary incontinence, baseline residual volume after voiding, or the proportion of participants who had not previously received anticholinergic therapy (Table 1).

EFFICACY

The mean reduction in episodes of urgency urinary incontinence per day was similar in the two groups over the course of months 1 through 6 (reduction of 3.4 episodes per day in the anticholinergic group and 3.3 in the onabotulinumtoxinA group, P=0.81). The reduction in daily episodes of urgency urinary incontinence was maintained in both groups for the 6-month active-treatment phase of the trial (Fig. 2). Only a small amount of data for the primary outcome was missing (9% of monthly follow-up diaries were missing), and missing data were evenly distributed between the treatment groups. The findings of a sensitivity analysis that was based on multiple imputation of missing data were consistent with those from the primary analysis.

We found no significant interactions between treatment group and either prior anticholinergic use (P=0.16) or baseline frequency of urgency urinary incontinence (P=0.53). However, a higher baseline frequency of episodes of urgency urinary

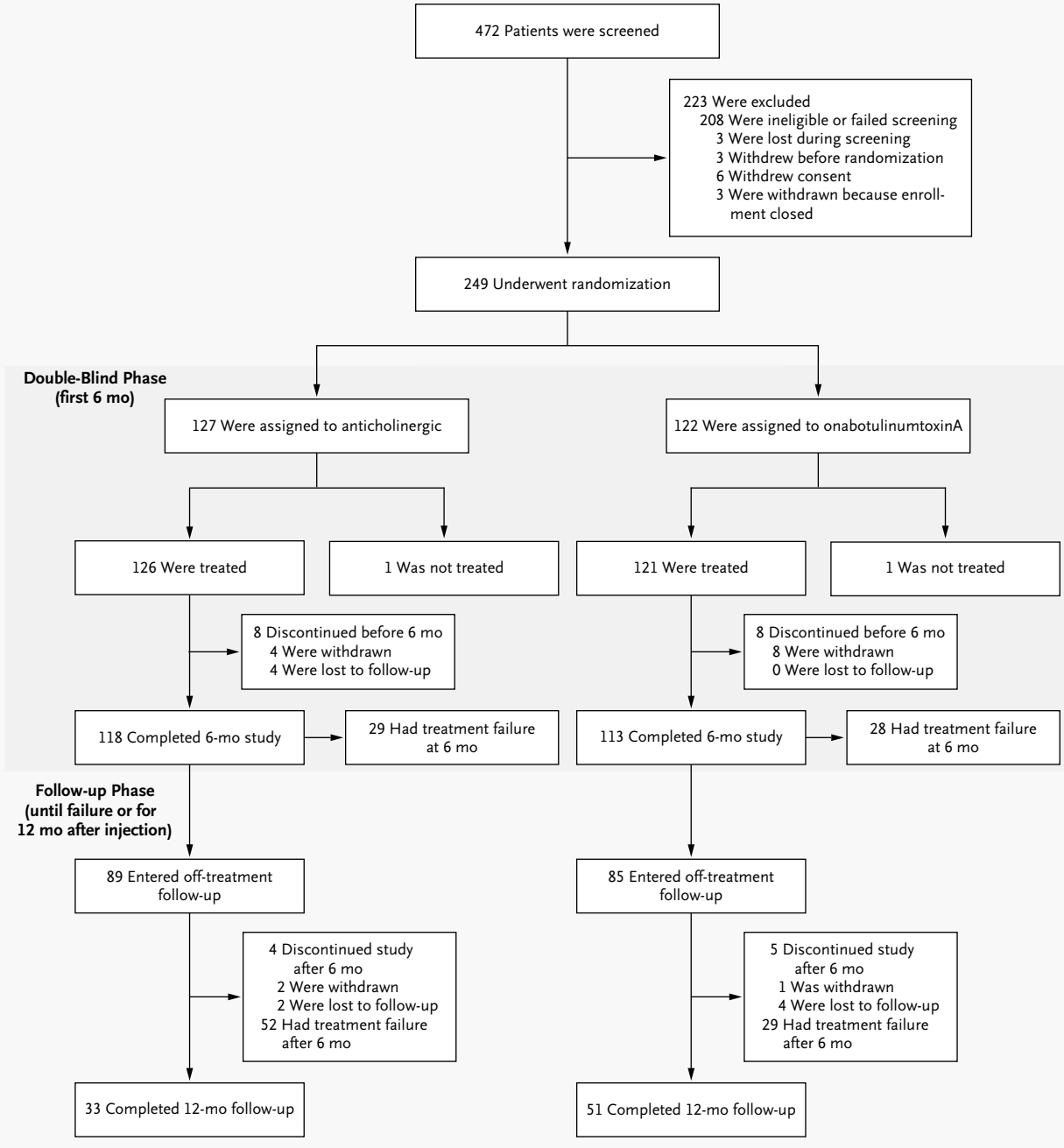

Figure 1. Screening, Randomization, Treatment, and Follow-up.

One of the 121 participants who was analyzed as treated with onabotulinumtoxinA (and placebo anticholinergic) was actually treated with active anticholinergic medication (and placebo onabotulinumtoxinA).

incontinence per day was associated with a greater reduction in episodes of urgency urinary incontinence (P<0.001).

Women in the onabotulinumtoxinA group were significantly more likely than those in the anticholinergic group to report complete resolution of urgency urinary incontinence (27% vs. 13%, P=0.003) (Table 2). Both groups had increases in scores on

Table 1. Baseline Characteristics of the Participants, According to Treatment Group.*

Characteristic	Anticholinergic Drug (N=126)	OnabotulinumtoxinA (N=121)
Age — yr	56.7±11.6	59.3±10.8
Hispanic ethnic group — no. (%)†	22 (17)	22 (18)
Race — no. (%)†		
White	98 (78)	96 (79)
Black	23 (18)	18 (15)
Other	5 (4)	7 (6)
Body-mass index‡	32.9±8.2	32.1±7.0
Marital status — no. (%)		
Married or living as married	57 (45)	58 (48)
Divorced, separated, or widowed	48 (38)	44 (36)
Single, never married	16 (13)	15 (12)
Other	1 (1)	0
Not reported	4 (3)	4 (3)
Educational level of at least some college	90 (71)	86 (71)
Type of health insurance — no. (%)		
Private only	60 (48)	61 (50)
Medicare or Medicaid only	16 (13)	10 (8)
Other only	34 (27)	28 (23)
Combination of several types	16 (13)	21 (17)
Not reported	0	1 (1)
Smoking status — no. (%)		
Never smoked	74 (59)	66 (55)
Previous smoker	40 (32)	39 (32)
Current smoker	12 (10)	15 (12)
Not reported	0	1 (1)
Menopausal status — no. (%)		
Premenopausal	22 (17)	15 (12)
Postmenopausal	92 (73)	102 (84)
Not sure	12 (10)	4 (3)
No prior anticholinergic therapy — no. (%)	54 (43)	48 (40)
Episodes of urgency incontinence — no./day§	5.2±2.7	4.8±2.7
Episodes of stress or urgency incontinence — no./day§	6.1±3.3	5.8±3.1
Residual volume after voiding — ml	35.4±47.4	36.6±44.6

* Plus–minus values are means ±SD. None of the characteristics differed significantly between the treatment groups.
† Race and ethnic group were self-reported.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ These variables were reported by the patient in 3-day diary entries.

the OABq-SF quality-of-life scale (indicating improved quality of life) and decreases in scores (indicating a positive effect on the participant) on the OABq-SF symptom-severity scale, the PFDI-SF, the PFIQ-SF, and the PGI-I. However, there were no significant between-group differences in the magnitudes of these improvements (Table 2).

Prespecified analyses of the trajectory of the response on the OABq-SF symptom-severity score, with response defined as a decrease in score by the minimal clinically important difference of 10 points,[12,13] showed that the time to initial response was rapid (1 month) and did not differ significantly between the groups (P=0.52). The

rates of response at months 1 and 2 were 87% and 95%, respectively, in the anticholinergic group and 91% and 96%, respectively, in the onabotulinumtoxinA group.

ADVERSE EVENTS

Dry mouth occurred in significantly more participants in the anticholinergic group than in the onabotulinumtoxinA group (46% vs. 31%, P=0.02) (Table 2). Intermittent catheterization was recommended according to protocol criteria at scheduled visits in the onabotulinumtoxinA group only (in 5% of the participants at 2 months, 3% at 4 months, and 1% at 6 months). However, additional women in both groups performed catheterization off-protocol (Table 2). More women in the onabotulinumtoxinA group than in the anticholinergic group had a urinary tract infection (33% vs. 13%, P<0.001). Serious adverse events, without regard to whether they were deemed to be related to treatment, were uncommon, and the rate did not differ significantly between the groups; none of the serious adverse events were considered by the investigators to be attributable to the study treatment (Table 2).

FOLLOW-UP AFTER CESSATION OF TREATMENT

At 6 months, 89 of the 126 participants (71%) who were randomly assigned to and received the anticholinergic medication and 85 of the 121 participants (70%) who were randomly assigned to and received onabotulinumtoxinA had adequate control of symptoms, as defined by a PGSC score of 4 or 5 and no off-study treatment for urgency urinary incontinence at or before 6 months, and entered the follow-up phase of the trial. At 6 months, all oral medications were discontinued. Within 1 month after discontinuation of the oral medication, significantly fewer women in the anticholinergic group than in the onabotulinumtoxinA group had adequate control of symptoms (50% vs. 62%, P=0.006). At 12 months, 25% in the anticholinergic group, as compared with 38% in the onabotulinumtoxinA group, had adequate control of symptoms (P=0.61) (Fig. 3).

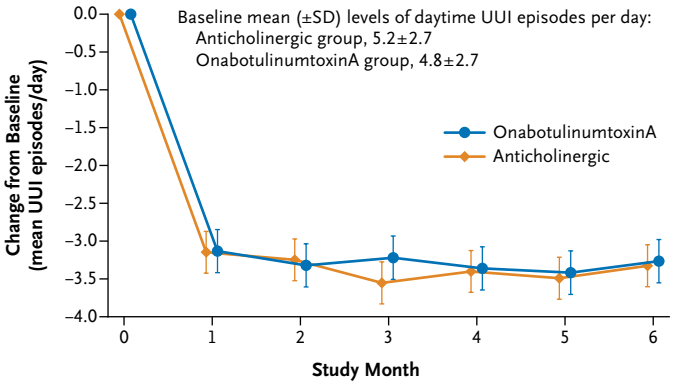

Figure 2. Reduction from Baseline in Number of Episodes of Urgency Urinary Incontinence (UUI) per Day.

The primary outcome of the study (the adjusted mean reduction from baseline in the number of episodes of urgency urinary incontinence per day) is shown in the modified intention-to-treat population, according to treatment group. I bars indicate 95% confidence intervals.

DISCUSSION

In this randomized, double-blind, comparative-effectiveness study, a standardized 6-month regimen of anticholinergic therapy and a single injection of 100 U of onabotulinumtoxinA each significantly reduced the number of daily episodes of urgency urinary incontinence; the magnitude of the reductions did not differ significantly between the treatments. Participants who received onabotulinumtoxinA, as compared with those who received anticholinergic therapy, more often had complete resolution of urgency urinary incontinence, whereas improvements in measures of quality of life did not differ significantly between the groups. The two treatments differ with respect to the method of administration: onabotulinumtoxinA is injected into the detrusor muscle by means of a cystoscopic procedure performed in a doctor's office, whereas anticholinergic therapy involves daily oral intake of pills prescribed by a physician. Side effects also differ. The frequency of dry mouth was higher in the anticholinergic group, whereas the frequencies of incomplete bladder emptying requiring catheterization and urinary tract infections were higher in the onabotulinumtoxinA group.

Although placebo-controlled, randomized trials have shown the efficacy of anticholinergic medications in treating urgency urinary incontinence, the high rate of side effects and poor long-term adherence associated with them limit their use in practice for some patients who have urgency urinary incontinence.[14-18] The rates of dry mouth in both groups in the current trial were higher than those reported in a Cochrane re-

view,[19] in which 31% of women taking anticholinergic agents and 10% of those taking placebo reported dry mouth. However, dry mouth was not a major cause of drug withdrawal — a finding similar to that in the Cochrane review — suggesting that the annoyance caused by this side effect is slight.

We were concerned that the efficacy of onabotulinumtoxinA might be counteracted by the side effect of urinary retention; we had stopped a previous placebo-controlled trial of onabotulinumtoxinA at a dose of 200 U early because the rate of urinary retention was 43%.[3] For the current study, we chose a lower dose of onabotulinumtoxinA — 100 U, a dose that was associated with an 18% risk of urinary retention (defined as a residual volume after voiding of >200 ml) and an 11% risk of intermittent catheterization in a recent dose-finding study.[20] We observed a lower rate of catheterization than this

Table 2. Secondary Outcomes: Efficacy, Quality of Life, and Adverse Events.

Outcome	Anticholinergic Drug	OnabotulinumtoxinA	P Value*
Efficacy outcome†			
Complete resolution of urgency urinary incontinence — no./total no. (%)‡	16/119 (13)	30/112 (27)	0.003
Complete resolution of all incontinence — no./total no. (%)‡	13/119 (11)	26/112 (23)	0.003
>75% reduction in episodes of urgency urinary incontinence — no./total no.(%)‡	48/119 (40)	61/112 (54)	0.06
Change from baseline in score on OABq-SF§			
Symptom-severity scale	−44.55	−44.08	0.87
Quality-of-life scale	37.05	37.13	0.98
Change from baseline in PFDI-SF total score¶	−43.69	−48.20	0.47
Change from baseline in PFIQ-SF total score‖	−32.82	−33.85	0.88
PGI-I — no./total no. (%)**			
Month 3	59/116 (51)	61/111 (55)	0.37
Month 6	67/116 (58)	60/111 (54)	0.71
Adverse events — no. of participants/total no. (%)††			
1 serious adverse event	6/127 (5)	4/120 (3)	0.70
Any adverse event	88/127 (69)	88/120 (73)	0.79
Dry mouth	58/127 (46)	37/120 (31)	0.02
Dry eyes	21/127 (17)	29/120 (24)	0.12
Constipation	36/127 (28)	25/120 (21)	0.06
Intermittent catheterization, per study criteria			
At 2 wk	0	10/111 (9)	<0.001
At 1 mo	0	3/112 (3)	0.11
At 2 mo	0	6/117 (5)	0.01
At 4 mo	0	3/111 (3)	0.11
At 6 mo	0	1/106 (1)	0.49
Self-catheterization since previous visit			<0.001
At 2 wk	4/121 (3)	9/118 (8)	0.16
At 1 mo	1/120 (1)	17/117 (15)	<0.001
At 2 mo	2/122 (2)	14/119 (12)	0.002
At 4 mo	1/121 (1)	11/112 (10)	0.003
At 6 mo	1/116 (1)	5/111 (5)	0.10

Table 2. (Continued.)

	Anticholinergic Drug	OnabotulinumtoxinA	P Value*
Urinary tract infection‡‡	16/127 (13)	40/120 (33)	<0.001
Residual volume after voiding >150 ml			<0.001
At 2 wk	7/120 (6)	33/111 (30)	<0.001
At 1 mo	6/115 (5)	30/112 (27)	<0.001
At 2 mo	6/119 (5)	23/117 (20)	<0.001
At 4 mo	9/119 (8)	17/111 (15)	0.05
At 6 mo	5/114 (4)	7/106 (7)	0.38

* P values were calculated with the use of longitudinal linear models for continuous measures assessed over time and longitudinal robust Poisson regression models for the binary outcome measures assessed over time, with adjustment for randomization strata where possible. For aggregate binary measures, P values were calculated with the use of Mantel–Haenszel tests with adjustment for randomization strata. Owing to zero cell counts for intermittent catheterization, P values were calculated for each visit independently, with the use of Fisher's exact test.

† Efficacy outcomes were assessed in the modified intention-to-treat population, which included all participants who underwent randomization and received a study medication and who had a baseline measure and at least one follow-up measure for the outcome. The modified intention-to-treat population comprised 126 participants in the anticholinergic-drug group and 121 in the onabotulinumtoxinA group.

‡ Proportions were based on data from participants who returned at least four follow-up diaries.

§ Values for the Overactive Bladder Questionnaire Short Form (OABq-SF) are changes from baseline in the adjusted mean scores for months 1 to 6. Scores on the OABq-SF range from 0 to 100, with higher scores on the symptom-severity scale indicating greater severity of symptoms and higher scores on the quality-of-life scale indicating better quality of life (see also Tables S1 and S2 in the Supplementary Appendix). Data were available for 123 participants in the anticholinergic-drug group and 119 in the onabotulinumtoxinA group.

¶ Values for Pelvic Floor Distress Inventory Short Form (PFDI-SF) are changes from baseline in the adjusted mean scores for months 3 to 6. Scores on the PFDI-SF range from 0 to 300, with higher scores indicating more symptoms and more bothersome symptoms. Data were available for 111 participants in the anticholinergic-drug group and 102 in the onabotulinumtoxinA group.

‖ Values for the Pelvic Floor Impact Questionnaire Short Form (PFIQ-SF) are changes from baseline in the adjusted mean scores for months 3 to 6. Scores on the PFIQ-SF range from 0 to 300, with higher scores indicating a more negative effect on activities, relationships, and feelings (see also Tables S1 and S2 in the Supplementary Appendix). Data were available for 111 participants in the anticholinergic-drug group and 102 in the onabotulinumtoxinA group.

** The Patient Global Impression of Improvement (PGI-I) is a patient-reported measure of perceived improvement with treatment, as assessed on a scale of 1 (very much better) to 7 (very much worse). Included here are participants who had adequate improvement, defined as a rating of 1 or 2 (much better).

†† The safety analyses were performed on data from all participants who underwent randomization and received a study medication, according to the actual treatment received. The safety population comprised 127 participants in the anticholinergic-drug group and 120 in the onabotulinumtoxinA group. (One of the 121 participants who was randomly assigned to onabotulinumtoxinA and placebo anticholinergic was treated with active anticholinergic medication and placebo onabotulinumtoxinA.) See Table S3 in the Supplementary Appendix for a list of all adverse events according to treatment group.

‡‡ A participant was considered to have a urinary tract infection if she had a urine culture that showed more than 100,000 colony-forming units per milliliter or received any antibiotic treatment for a urinary tract infection.

according to prespecified criteria in our study. However, additional off-protocol catheterizations were performed in both groups, perhaps in part because we warned the participants of the potential for urinary retention. Our results indicate that a 100-U dose of onabotulinumtoxinA is effective and has manageable side effects in this population of women with urgency urinary incontinence and without known neurologic conditions. Further study is needed to determine whether a higher dose of onabotulinumtoxinA would be appropriate for women with urgency urinary incontinence that is more severe than that in the women in our study or that is refractory to other therapy.

In the Cochrane review,[19] which encompassed 61 trials, the mean reduction in episodes of urgency urinary incontinence per day ranged from 0.6 to 1.7 among people receiving anticholinergic medications and between 0.1 and 1.9 among those receiving placebo, with 0.54 fewer episodes per day among participants receiving the anticholinergic medications than among those receiving placebo. The greater reduction in episodes observed in both groups in our study may be due to the higher baseline severity in our population.

We chose the oral medications for this trial on the basis of several considerations, including the option for dose escalation of the initial drug and, if necessary, a switch to a second drug that had mechanisms of action different from the

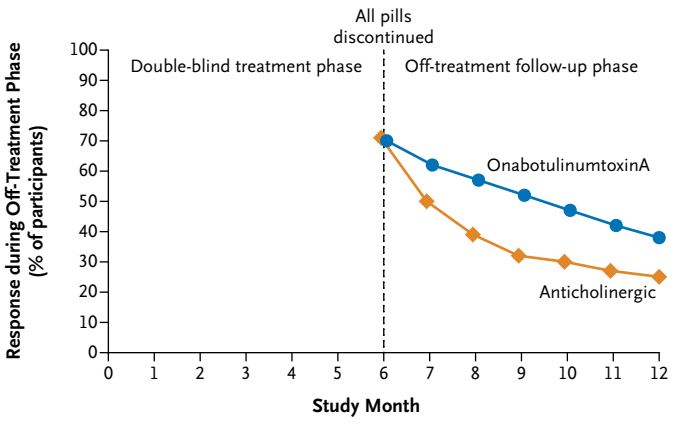

Figure 3. Adequate Control of Symptoms during Off-Treatment Follow-up.

The percentage of participants who had adequate control of symptoms during a 6-month off-treatment follow-up phase is shown in the modified intention-to-treat population, according to the treatment group to which the participants had been randomly assigned at the beginning of the study. Adequate control was defined as a score of 4 or 5 on the Patient Global Symptom Control (PGSC) instrument and no off-study treatment for urinary incontinence at prior visits. Responses on the PGSC to the statement, "This treatment has given me adequate control of my urinary leakage" range from 1 (disagree strongly) to 5 (agree strongly).

first but that was administered in the same way (orally, once daily). Solifenacin is a relatively selective M3 antagonist, and trospium has nonselective muscarinic activity, had recently become available in once-daily dosing, and has been associated with a low rate of dry mouth (8.7%).[6] Although it is uncertain whether our results are generalizable to other anticholinergic drugs, systematic reviews report few clinically significant differences among currently available anticholinergic drugs.[2]

The randomized, controlled design that includes two active-treatment groups and an effective double-blind procedure improves our ability to interpret our primary comparison. The inclusion of participants who had not had prior exposure to anticholinergic medications as well as those who had had prior exposure to up to two anticholinergic medications, the inclusion in the study of participants from multiple sites, and the broad eligibility criteria facilitate the generalizability of our study findings. Since we studied a single injection of one formulation of botulinum toxin A (onabotulinumtoxinA at a dose of 100 U), we are unable to comment on the safety or efficacy of other botulinum toxin preparations or on effects of multiple injections of onabotulinumtoxinA as compared with longer-term anticholinergic therapy. Prior studies have shown that effectiveness is maintained after multiple injections of onabotulinumtoxinA into the detrusor muscle and that the mean interval between injections (265 days) is not reduced with repeated injections.[21,22] Since our trial compared two active treatments, we cannot determine to what extent the observed improvements reflect a placebo effect. However, the observed rates of cure or improvement observed in our study exceed the placebo effect observed in trials of anticholinergic drugs.[19] Further research is needed to compare patient adherence and the cost-effectiveness of these two therapeutic approaches.

In summary, we found that among women with urgency urinary incontinence, there was no significant difference between anticholinergic drugs and onabotulinumtoxinA by injection on the reduction of the frequency of episodes of urgency incontinence or improvements in quality of life. The choice between these therapies should take into account the differing regimens and routes of administration and the side-effect profiles, including more frequent occurrence of dry mouth with anticholinergic medication and higher risks of intermittent catheterization and urinary tract infection with onabotulinumtoxinA.

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REFERENCES

1. Stewart WF, Van Rooyen JB, Cundiff GW, et al. Prevalence and burden of overactive bladder in the United States. World J Urol 2003;20:327-36.
2. Hartmann KE, McPheeters ML, Biller DH, et al. Treatment of overactive bladder in women. Evid Rep Technol Assess (Full Rep) 2009;187:1-120.
3. Brubaker L, Richter HE, Visco A, et al. Refractory idiopathic urge urinary incontinence and botulinum A injection. J Urol 2008;180:217-22.
4. Visco AG, Brubaker L, Richter HE, et al. Anticholinergic versus botulinum toxin A comparison trial for the treatment of bothersome urge urinary incontinence: ABC trial. Contemp Clin Trials 2012;33:184-96.
5. Chapple CR, Arano P, Bosch JL, De Ridder D, Kramer AE, Ridder AM. Solifenacin appears effective and well tolerated in patients with symptomatic idiopathic detrusor overactivity in a placebo- and tolterodine-controlled phase 2 dose-finding study. BJU Int 2004;93:71-7. [Erratum, BJU Int 2004;93:1135.]
6. Staskin D, Sand P, Zinner N, Dmochowski R. Once daily trospium chloride is effective and well tolerated for the treatment of overactive bladder: results from a multicenter phase III trial. J Urol 2007;178:978-83.
7. Brubaker L, Kreder L, Richter HE, et al. Refractory Urge Urinary Incontinence and Botulinum A Injection: the methods of the RUBI Trial. J Appl Res 2006;6:260-71.
8. Matza LS, Thompson CL, Krasnow J, Brewster-Jordan J, Zyczynski T, Coyne KS. Test-retest reliability of four questionnaires for patients with overactive bladder: the Overactive Bladder Questionnaire (OAB-q), Patient Perception of Bladder Condition (PPBC), Urgency Questionnaire (UQ), and the Primary OAB Symptom Questionnaire (POSQ). Neurourol Urodyn 2005;24:215-25.
9. Coyne KS, Matza LS, Thompson C, Jumadilova Z, Bavendam T. The responsiveness of the OAB-q among OAB patient subgroups. Neurourol Urodyn 2007;26:196-203.
10. Barber MD, Walters MD, Bump RC. Short forms of two condition-specific quality-of-life questionnaires for women with pelvic floor disorders (PFDI-20 and PFIQ-7). Am J Obstet Gynecol 2005;193:103-13.
11. Yalcin I, Bump RC. Validation of two Global Impression questionnaires for incontinence. Am J Obstet Gynecol 2003;189:98-101.
12. Coyne KS, Matza LS, Thompson CL, Kopp ZS, Khullar V. Determining the importance of change in the Overactive Bladder Questionnaire. J Urol 2006;176:627-32.
13. Dyer KY, Xu Y, Brubaker L, et al. Minimum important difference for validated instruments in women with urge incontinence. Neurourol Urodyn 2011;30:1319-24.
14. Diokno AC, Sand PK, Macdiarmid S, Shah R, Armstrong RB. Perceptions and behaviours of women with bladder control problems. Fam Pract 2006;23:568-77.
15. Shaya FT, Blume S, Gu A, Zyczynski T, Jumadilova Z. Persistence with overactive bladder pharmacotherapy in a Medicaid population. Am J Manag Care 2005;11:Suppl:S121-S129.
16. Yu YF, Nichol MB, Yu AP, Ahn J. Persistence and adherence of medications for chronic overactive bladder/urinary incontinence in the California Medicaid program. Value Health 2005;8:495-505.
17. Herschorn S, Becker D, Miller E, Thompson M, Forte L. Impact of a health education intervention in overactive bladder patients. Can J Urol 2004;11:2430-7.
18. Kelleher CJ, Cardozo LD, Khullar V, Salvatore S. A medium-term analysis of the subjective efficacy of treatment for women with detrusor instability and low bladder compliance. Br J Obstet Gynaecol 1997;104:988-93.
19. Nabi G, Cody JD, Ellis G, Herbison P, Hay-Smith J. Anticholinergic drugs versus placebo for overactive bladder syndrome in adults. Cochrane Database Syst Rev 2006;4:CD003781.
20. Dmochowski R, Chapple C, Nitti VW, et al. Efficacy and safety of onabotulinumtoxinA for idiopathic overactive bladder: a double-blind, placebo controlled, randomized, dose ranging trial. J Urol 2010;184:2416-22.
21. Gordon MF, Barron R. Effectiveness of repeated treatment with botulinum toxin type A across different conditions. South Med J 2006;99:853-61.
22. Karsenty G, Reitz A, Lindemann G, Boy S, Schurch B. Persistence of therapeutic effect after repeated injections of botulinum toxin type A to treat incontinence due to neurogenic detrusor overactivity. Urology 2006;68:1193-7.