Characteristics Associated with Treatment Response and Satisfaction in Women Undergoing OnabotulinumtoxinA and Sacral Neuromodulation for Refractory Urgency Urinary Incontinence

Holly E. Richter,^{*,†} C. L. Amundsen, S. W. Erickson, J. E. Jelovsek, Y. Komesu, C. Chermansky,[‡] H. S. Harvie, M. Albo, D. Myers, W. T. Gregory and D. Wallace for the NICHD Pelvic Floor Disorders Network

EQ1 From the University of Alabama at Birmingham (HER), Birmingham, Alabama, Duke University (CLA), Durham and RTI International (SWE, DW), Research Triangle Park, North Carolina, Cleveland Clinic (JEJ), Cleveland, Ohio, University of New Mexico (YK), Albuquerque, New Mexico, Magee-Womens Research Institute, University of Pittsburgh (CC), Pittsburgh and University of Pennsylvania (HSH), Philadelphia, Pennsylvania, University of California-San Diego (MA), San Diego, California, Brown University (DM), Providence, Rhode Island, and Oregon Health and Science University (WTG), Portland, Oregon

Purpose: We sought to identify clinical and demographic characteristics associated with treatment response and satisfaction in women undergoing onabotulinumtoxinA and sacral neuromodulation therapies.

Materials and Methods: We analyzed data from the ROSETTA (Refractory Overactive Bladder: Sacral NEuromodulation versus BoTulinum Toxin Assessment) trial. Baseline participant characteristics and clinical variables were associated with 2 definitions of treatment response, including 1) a reduction in mean daily urgency incontinence episodes during 6 months and 2) a 50% or greater decrease in urgency incontinence episodes across 6 months. The OAB-S (Overactive Bladder-Satisfaction) questionnaire was used to assess satisfaction.

Results: A greater reduction in mean daily urgency incontinence episodes was associated with higher HUI-3 (Health Utility Index-3) scores in the onabotulinumtoxinA group and higher baseline incontinence episodes (each $p < 0.001$) in the 2 groups. Increased age was associated with a lesser decrease in incontinence episodes in the 2 groups ($p < 0.001$). Increasing body mass index (adjusted OR 0.82/5 points, 95% CI 0.70–0.96) was associated with reduced achievement of a 50% or greater decrease in incontinence episodes after each treatment. Greater age (adjusted OR 0.44/10 years, 95% CI 0.30–0.65) and a higher functional comorbidity index (adjusted OR 0.84/1 point, 95% CI 0.71–0.99) were associated with reduced achievement of a 50% or greater decrease in urgency incontinence episodes in the onabotulinumtoxinA group only ($p < 0.001$ and 0.041,

Abbreviations and Acronyms

BMI = body mass index
FCI = Functional Comorbidity Index
HRQoL = health related QoL
HUI-3 = Health Utility Index-3
OABq = Overactive Bladder Questionnaire
OABq-SF = OABq-Short Form
QoL = quality of life
ROSETTA = Refractory Overactive Bladder: Sacral NEuromodulation versus BoTulinum Toxin Assessment
SNM = sacral neuromodulation
UIE = urinary incontinence episode
UUI = urgency urinary incontinence
UUIE = UUI episode

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* Correspondence: 1700 6th Av. South, Suite 10382, Birmingham, Alabama 35233 (telephone: 205-934-1704; FAX: 205-975-8893; e-mail: hrichter@uabmc.edu).

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respectively). In the onabotulinumtoxinA group increased satisfaction was noted with higher HUI score ($p = 0.002$) but there was less satisfaction with higher age ($p = 0.001$).

Conclusions: Older women with multiple comorbidities, and decreased functional and health related quality of life had decreased treatment response and satisfaction with onabotulinumtoxinA compared to sacral neuromodulation for refractory urgency incontinence.

Key Words: urinary bladder; urinary incontinence, urge; onabotulinumtoxinA; electric stimulation; quality of life

WOMEN with UUI refractory to primary treatment approaches, including medications and behavioral therapy, may be offered third line treatment options such as posterior tibial nerve stimulation, SNM or onabotulinumtoxinA. Understanding patient clinical and demographic characteristics potentially associated with the third line treatment response, especially in the setting of more invasive treatment approaches such as SNM and onabotulinumtoxinA, is important and may help optimize treatment success.

The ROSETTA trial was an open label, randomized trial in women with idiopathic refractory UUI who were randomized to onabotulinumtoxinA or SNM.¹ The objective of this planned secondary analysis was to identify baseline clinical and demographic factors associated with treatment response and satisfaction in women participating in this multicenter randomized trial.

MATERIALS AND METHODS

The design and primary results of the ROSETTA trial have been previously published.^{1,2} The institutional review board at each clinical site and coordinating center approved the protocol and participants provided written informed consent. Major inclusion criteria for women participating in the ROSETTA trial included a minimum of 6 UIIEs on a baseline 3-day bladder diary, not taking or stopping UUI medications at least 3 weeks prior to the baseline evaluation and urodynamic assessment within 18 months before randomization. Standardized demographic, clinical data and key procedural elements were collected at baseline.

Briefly, participants randomized to SNM underwent stage 1 lead placement by experienced surgeons in the operating suite. During the 7 to 14-day testing phase participants with 50% or greater improvement in mean UIIE on a 3-day bladder diary were categorized as clinical responders and were eligible for placement of the permanent implantable pulse generator. Those without this improvement had the lead removed. Participants randomized to onabotulinumtoxinA received a single cystoscopic intradetrusor injection of 200 U performed in clinic. Women with a 50% or greater reduction in UIIE on a bladder diary 1 month after injection were defined as onabotulinumtoxinA clinical responders.

Treatment response outcomes for this planned secondary analysis included 1) a reduction in mean daily

UIIEs averaged across 6 months, 2) a 50% or greater decrease in UIIE on each completed diary across 6 months as recorded in monthly 3-day bladder diaries and 3) treatment satisfaction on OAB-SATq (Overactive Bladder Satisfaction with Treatment Questionnaire).²

All participants with 1 to 6 post-baseline diaries were included in the mean daily UIIE analyses while only participants with at least 4 completed diaries were included in the 50% or greater decrease analyses. The potential variables thought to be associated with treatment response were sociodemographic characteristics, including age in years and race/ethnicity; medical history and functional status, including BMI as a continuous variable, smoking status, menopausal status, and the Timed Up and Go test; characteristics of urinary incontinence, including UIIE, Sandvik score and UDI-SF (Urogenital Distress Inventory-Short Form); symptom impact and incontinence related quality of life on OABq-SF and IIQ-SF (Incontinence Impact Questionnaire-Short Form), and health related quality of life on HUI-3; and urodynamic variables and medical comorbidities, including history of recurrent urinary tract infections and FCI.^{2,3}

To identify variables associated with a reduction in mean daily UIIEs during 1 to 6 months after treatment as a continuous outcome we fit linear mixed models for each potential predictor, controlling for treatment group, age group (less than 65 and 65 years or greater), site, month after treatment and interaction of treatment group with month. Person-month was used as the unit of analysis. Participants were treated as a random effect to account for the within subject correlation with time.

To evaluate whether the impact of the potential predictors differed by treatment group the models were fit with a treatment by predictor interaction term. To identify baseline variables associated with a 50% or greater reduction in UIIEs as a dichotomous outcome logistic regression models were fit for each potential predictor with all models controlling for treatment group and age group as factors included in the original randomization. An analogous linear model was used to examine the effect of predictors on treatment satisfaction using OAB-SATq at 6 months.

Initially each baseline variable was modeled individually to assess associations with each outcome. Parameter estimates, ORs and 95% CIs were generated by treatment group based on treatment stratified analyses. Variables in which the main effect or the interaction term was at $p < 0.10$ using the Wald test were included as candidate terms in a combined multivariable model. That model

then underwent backward variable selection so that each term in the final multivariable model was at $p < 0.10$. Results were not adjusted for multiple comparisons and all p values should be interpreted accordingly. Analyses were performed with SAS®, version 9.4.

RESULTS

A total of 190 participants randomized to onabotulinumtoxinA and 174 randomized to SNM were included in this secondary analysis. Baseline characteristics were similar in the treatment groups (supplementary table 1, <http://jurology.com/>). Overall mean $\pm$ SD age was 63.0 ± 11.6 years and mean body mass index was 32.2 ± 8.2 kg/m². Participants reported a mean of 5.30 ± 2.67 UIEs per day and 96% reported that UUI symptoms were moderate or greater on the Sandvik questionnaire. Supplementary table 1 (<http://jurology.com/>) lists other characteristics.

The reduction in mean daily UIEs during 6 months was not associated with most baseline covariates on univariable analysis. However, increasing age and higher (better) baseline OABq-SF QoL score were associated with a lesser decrease in mean daily UIEs during 6 months (supplementary table 2, <http://jurology.com/>). Hispanic/Latina ethnicity, detrusor overactivity on cystometrogram, a greater number of daily UIEs and total UIEs per day, higher (worse) OABq-SF symptom bother scores and higher (better) HUI-3 scores were associated with a greater reduction in mean daily UIEs.

A greater effect was noted in the onabotulinumtoxinA group for UIEs and total UIEs. Multivariable analyses revealed that age and greater baseline UIE frequency in the onabotulinumtoxinA and SNM groups were associated with a UIE reduction (tables 1 to 3). For age there was an

average decrease in reduction of about 0.3 UIEs per day for each added decade of age. For greater baseline UIE frequency there was an increased reduction of 0.6 UIEs per day for each unit increase in baseline UIEs, ie an increased reduction of approximately 60% of the incremental level. Increasing age was associated with a lower treatment response while higher frequency of baseline UIEs was associated with an increased treatment response. Higher HUI-3 score was also associated with an improved treatment response with some evidence of a greater reduction in UIEs in the onabotulinumtoxinA group.

Similarly univariable analysis of the achievement of a 50% or greater reduction in UIEs revealed that increased age, higher BMI, higher (worse) FFCI score, higher (worse) baseline IIQ-SF score and higher (worse) Sandvik score were associated with decreased odds (supplementary table 3, <http://jurology.com/>). Greater volume at maximum cystometric capacity and higher (better) HUI-3 score were associated with increased odds of achieving a 50% or greater reduction in UIEs. A greater effect (lower OR) was noted in the onabotulinumtoxinA group for FCI.

On multivariable analysis increasing age and higher BMI were associated with decreased odds of achieving a treatment response of a 50% or greater reduction in UIEs with the effect of age greater in the onabotulinumtoxinA group. Higher FCI score was associated with decreased odds of achieving a 50% or greater reduction in UIEs only in the onabotulinumtoxinA group.

Univariable analysis revealed that for each treatment greater age, UIEs per day, total UIEs per day and Sandvik score were associated with decreased treatment satisfaction, as was Latina ethnicity (supplementary table 4, <http://jurology.com/>). African American race was associated with

Table 1. Multivariable associations between participant characteristics and reduction in mean daily urgency urinary incontinence episodes in posttreatment months 1 to 6

	Coefficient (95% CI)		p Value	
	OnabotulinumtoxinA	Sacral Neuromodulation	Main Predictor Effect	Treatment $\times$ Predictor
Mean UIEs/day reduction:*				
No. pts	190	174	—	—
HUI-3/0.30 points†	0.50 (0.23–0.77)	0.09 (–0.21–0.40)	0.004	0.051
OABq treatment satisfaction:‡				
No. pts	150	129	—	—
Age/decade	–6.53 (–10.39––2.68)	–0.69 (–4.86–3.47)	0.015	0.039
HUI-3/0.30 points	6.84 (2.48–11.19)	0.41 (–4.79–5.60)	0.039	0.059

* Final model included HUI-3 per 0.1 point, age in decades to generate meaningful effect estimates (age included in model as continuous variable in years) and UIEs per day.

† HUI-3 baseline standard deviation in our study population and HUI-3 effect in onabotulinumtoxinA and sacral neuromodulation groups $p < 0.001$ and $p = 0.545$, respectively.

‡ Final model included HUI-3 per 0.1 point (baseline standard deviation in our study population), age in decades, UIEs and stress UIEs per day, and race, and age and HUI-3 effects of $p = 0.001$ and 0.002 in onabotulinumtoxinA group, and $p = 0.744$ and 0.878 , respectively, in sacral modulation group.

Table 2. Multivariable associations between participant characteristics and reduction in mean daily urgency urinary incontinence episodes in posttreatment months 1 to 6

	OnabotulinumtoxinA + Sacral Neuromodulation Coefficient (95% CI)	Main Predictor Effect p Value
<i>Mean UIEs/day reduction*</i>		
No. pts	364	—
Age/decade	−0.32 (−0.49—−0.15)	<0.001
No. UIEs/day	0.62 (0.54—0.70)	<0.001
<i>OABq treatment satisfaction†</i>		
No. pts	279	—
Race:		
African American	14.62 (3.41—25.83)	0.017
Other	−6.91 (−19.87—6.05)	
Caucasian	Referent	
No. UIEs/day:		
Urgency	−1.89 (−3.25—−0.54)	0.006
Stress	−4.65 (−8.81—−0.49)	0.029

* Final model included HUI-3 score per 0.1 points, age in decades to generate meaningful effect estimates (age included in model as continuous variable in years) and urgency urinary incontinence episodes per day.

† Final model included HUI-3 score per 0.1 points, age in decades to generate meaningful effect estimates (age included in model as continuous variable in years), UIEs per day, stress UIEs per day and race.

increased satisfaction relative to Caucasian race. Increased HUI score was associated with increased satisfaction in the onabotulinumtoxinA group.

Multivariable analysis revealed that in each treatment group African American race was associated with increased satisfaction, and increased UIEs per day and stress UIEs per day with decreased satisfaction. Increased age was associated with decreased satisfaction, a higher HUI score and

Table 3. Multivariable associations of participant characteristics with 50% or greater UIIE reduction during 6 months

	Adjusted OR (95% CI)
No. pts.*	
OnabotulinumtoxinA	178
Sacral neuromodulation	166
Age (decades):†	
OnabotulinumtoxinA	0.44 (0.30—0.65)
Sacral neuromodulation	0.78 (0.57—1.08)
Main predictor effect p value	<0.001
Treatment × predictor p value	0.016
OnabotulinumtoxinA + sacral neuromodulation:	
BMI kg/m ² /5 points	0.82 (0.70—0.96)
Main predictor effect p value	0.013
IIQ/10 points	0.91 (0.82—1.00)
Main predictor effect p value	0.062
Sandvik score	0.92 (0.84—1.01)
Main predictor effect p value	0.068

Final model included age in decades to generate meaningful effect estimates (age included in model as continuous variable in years), FCI per per point, body mass index in kg/m² per 5 points, IIQ per 10 points and Sandvik score.

* Patients completed at least 4 bladder diaries.

† In onabotulinumtoxinA group age effect p <0.001 and FCI effect p = 0.041, and in sacral neuromodulation group p = 0.137 and 0.385, respectively.

greater satisfaction with onabotulinumtoxinA treatment.

DISCUSSION

In this planned secondary analysis of women with refractory UUI randomized to onabotulinumtoxinA or SNM increasing age was associated with a lesser mean reduction (less efficacy) while higher baseline HUI-3 score and UIEs were associated with an increased mean reduction (greater efficacy) in UIEs per day with the HUI-3 effect greater in the onabotulinumtoxinA group. Similarly regarding the outcome of a 50% or greater reduction in UIEs increasing age and higher BMI were associated with decreased odds of a treatment response in all participants. A higher FCI score conferred decreased odds only in the onabotulinumtoxinA group.

These 2 specific treatment outcomes were studied since they are commonly reported in the onabotulinumtoxinA and SNM literature. Overall treatment satisfaction with these third line therapies was associated with African American race and decreased satisfaction was associated with increased UIEs and stress UIEs. Similar to treatment responsiveness increased age was associated with less satisfaction in the onabotulinumtoxinA group. Better health related QOL was associated with greater satisfaction with onabotulinumtoxinA therapy.

Increasing age was independently associated with a poorer treatment response to each treatment and for each UIIE treatment response definition used in this study. The age association suggests that lower urinary tract changes which develop with aging, including decreased urethral closure pressure and detrusor contractility, and increased detrusor overactivity, may predispose older women to a UUI phenotype that may be more refractory to treatment.^{4–6}

To provide perspective on average a 55-year-old woman would have an increased mean reduction of 0.64 UIEs per day compared to a 65-year-old woman. In the onabotulinumtoxinA group a 55-year-old woman would have about twice the odds of achieving a 50% or greater reduction in UIEs compared to a 65-year-old woman. The effect of age in previous reports of SNM treatments has varied. Prior SNM studies described older women gaining benefit from SNM but showed higher continence rates and a greater UIIE reduction in the younger group.^{7,8} In contrast, Peters et al prospectively evaluated 328 patients, of whom 83% were women, and found that SNM success was not age dependent.⁹ Including an urgency only population and pudendal neuromodulation may have affected the latter results.

Less information exists regarding the effect of age on onabotulinumtoxin A treatment response and satisfaction. One group reported results in 27 patients with refractory UI in the onabotulinumtoxin A and SNM groups. Higher baseline HUI-3 scores were associated with a better treatment response. For example, a woman with a baseline HUI-3 score of 0.7 would experience an average reduction of 0.5 episodes per day more compared to a woman with a baseline score of 0.4. This represents a difference of 0.3 in HUI-3 score, which is approximately the baseline standard deviation in our study population and is 10 times the reported minimally important difference of 0.03.¹⁷

Women with higher health related quality of life had a greater improvement in the mean daily reduction in UIEs during 6 months in each treatment group with greater decrease in the onabotulinumtoxin A group. This may reflect a differential impact of incontinence on general health status and HRQoL, and a greater chance of treatment benefit. The trend toward a greater beneficial effect of a higher HUI-3 score on the success of onabotulinumtoxin A is unclear. Further research is again warranted to understand the particular interaction between botulinum toxin and health status.

Finally, with respect to FCI and its association with a 50% or greater reduction in UIEs in the onabotulinumtoxin A group, women with more medical comorbidities have a greater likelihood of increased incontinence severity.^{18,19} In the current study a woman with a baseline FCI score of 1 would have approximately 70% greater odds of achieving a 50% or greater reduction in UIEs than a woman with a baseline score of 4. Assessment of baseline physical function and HRQoL status as measured by FCI is important since it may be used to control for baseline comorbidity, provide a perspective on potential return to functional levels after treatment and serve as a predictor of outcome.²⁰ Incontinence treatment may be more difficult in women with more morbidities due to the potential cumulative negative impact on daily functioning and bladder control. This was previously noted in 105 men and women in whom decreased SNM cure rates were associated with having 3 or more chronic medical conditions regardless of age.⁸ It is unclear why we found a differential treatment effect for onabotulinumtoxin A. As with HUI-3, further evaluation is needed to better understand this specific finding.

Our planned secondary analysis had several strengths. It allowed robust assessment of a large number of women who met standardized criteria for refractory UI with clearly defined preoperative clinical and demographic variables, and validated outcome measures, treatment outcomes and satisfaction. Study limitations include a followup limited

In the current study we found that increased baseline BMI decreased the odds of achieving a 50% or greater UIE reduction. For example, the model estimated that a woman with a BMI of 25 kg/m² would have about 50% greater odds of achieving a 50% or greater reduction in UIEs than a woman with a BMI of 35 kg/m². This is consistent with prior epidemiological literature in which increasing BMI was associated with UI severity.^{11,12} Determining the association of BMI for predicting treatment success is important because it is a modifiable risk factor. Each 5-point increase in baseline BMI decreased the odds of attaining a 50% or greater UIE reduction by approximately 20%. Alternatively a woman with a BMI of 25 kg/m² would have about 50% greater odds of achieving a 50% or greater reduction in UIEs than a woman with a BMI of 35 kg/m², assuming that all other covariates were the same. Subak et al found that weight loss after bariatric surgery was associated with substantially decreased urinary incontinence during 3 years.¹³ Further research is needed of the role of weight loss in UI refractory to treatment.

Other characteristics associated with treatment response included the baseline number of UIEs per day and HUI-3 in the overall reduction in mean daily UIEs. Women with higher baseline UIEs per day experienced a greater mean decrease in UIEs per day. This finding reinforces previous results, including those in a randomized trial of anticholinergic therapy vs onabotulinumtoxin A¹⁴ and another describing the results of SNM testing.¹⁵

HUI-3 is an instrument used to measure general health status and HRQoL which is scored on a scale of 0.00—death to 1.00—perfect health.² HUI-3 has been noted to provide valid measurements for utility scores in women with stress, urgency and mixed

urinary incontinence.¹⁶ In our study HUI-3 demonstrated responsiveness to a change in the treatment of refractory UI in the onabotulinumtoxin A and SNM groups. Higher baseline HUI-3 scores were associated with a better treatment response. For example, a woman with a baseline HUI-3 score of 0.7 would experience an average reduction of 0.5 episodes per day more compared to a woman with a baseline score of 0.4. This represents a difference of 0.3 in HUI-3 score, which is approximately the baseline standard deviation in our study population and is 10 times the reported minimally important difference of 0.03.¹⁷

Women with higher health related quality of life had a greater improvement in the mean daily reduction in UIEs during 6 months in each treatment group with greater decrease in the onabotulinumtoxin A group. This may reflect a differential impact of incontinence on general health status and HRQoL, and a greater chance of treatment benefit. The trend toward a greater beneficial effect of a higher HUI-3 score on the success of onabotulinumtoxin A is unclear. Further research is again warranted to understand the particular interaction between botulinum toxin and health status.

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Our planned secondary analysis had several strengths. It allowed robust assessment of a large number of women who met standardized criteria for refractory UI with clearly defined preoperative clinical and demographic variables, and validated outcome measures, treatment outcomes and satisfaction. Study limitations include a followup limited

to 6 months and the inclusion of only women participants.

CONCLUSIONS

Older women with multiple comorbidities, and decreased functional and health related QoL had reduced treatment response and satisfaction with onabotulinumtoxinA compared to sacral neuromodulation for refractory urgency incontinence. Increasing BMI was associated with a decreased response to each treatment. This information may help individualize treatment approaches for these more invasive third line therapies.

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EDITORIAL COMMENT

In this preplanned secondary analysis of the ROSETTA trial¹ Richter et al state that higher age and a higher comorbidity index were associated with a decreased response rate to onabotulinumtoxinA injections on multivariable analysis. This relatively new finding again raises the issue of patient selection when considering second line management of overactive bladder.

One important limitation of the analysis is that women with nonneurogenic (but maybe not idiopathic) overactive bladder were included. Indeed, nonneurogenic overactive bladder is rather a multifactorial disease with poorly understood underlying causes. Bowel disease, pelvic organ chronic dysfunction or crosstalk, asymptomatic neurological diseases, an autonomous nervous

system imbalance, concomitant medications, the brain-bladder axis, urinary microbiota, psychological conditions and several other factors with unclear respective roles might explain overactive bladder and influence treatment outcomes. Refining our diagnostic approach might be the price to pay to better select patients and make a step forward in this field.

Jean-Nicolas Cornu*

*Charles Nicolle University Hospital
Rouen Cedex, France*

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