Persistent Therapeutic Effect of Repeated Injections of Onabotulinum Toxin A in Refractory Bladder Pain Syndrome/Interstitial Cystitis

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Abbreviations and Acronyms

BPS/IC = bladder pain syndrome/interstitial cystitis
FVC = 3-day frequency volume chart
OnabotA = onabotulinum toxin A
OSS = O'Leary-Sant score
QoL = quality of life
UTI = urinary tract infection
VAS = 10-point visual analogue scale

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Purpose: We evaluate the efficacy and safety of repeated intratrigonal injections of onabotulinum toxin A in patients with bladder pain syndrome/interstitial cystitis.
Materials and Methods: This is a single center, long-term, prospective study in which 16 women with bladder pain syndrome/interstitial cystitis refractory to standard treatment received 4 consecutive intratrigonal injections of onabotulinum toxin A. Onabotulinum toxin A (100 U) was injected under cystoscopic control in 10 trigonal sites, each receiving 10 U in 1 ml saline. General anesthesia was used in all treatments. Re-treatment was allowed 3 months after injection. Outcome measures included pain visual analog scale (0–10), O'Leary-Sant score, a 3-day voiding chart and a quality of life questionnaire at the first month and every 3 months after each injection. Voiding dysfunction and urinary tract infections were assessed at 2 weeks and every 3 months afterward. Treatment duration was determined when patients requested another injection.
Results: Mean ± SD patient age was 41.8 ± 12.5 years. At baseline pain score was 5.9 ± 1.8, O'Leary-Sant score 28.8 ± 6.3, urinary frequency 16.4 ± 5.3, mean voided volume 112 ± 42 ml and quality of life 5 ± 0.9. Mean decrease in pain score, O'Leary-Sant score, urinary frequency and mean increase in voided volume and quality of life were similar after each treatment. Individual symptom relief lasted 6 to 12 months with an average duration of 9.9 ± 2.4 months. There were no cases of voiding dysfunction. Five patients had noncomplicated urinary tract infections.
Conclusions: Symptomatic improvement of bladder pain syndrome/interstitial cystitis persists in a repeated intratrigonal injection program of 100 U onabotulinum toxin A. Time to request re-treatment remained stable. Adverse events were mild, without voiding dysfunction requiring intermittent catheterization.

Key Words: cystitis, interstitial; onabotulinumtoxinA; urinary bladder; pain

Bladder pain syndrome/interstitial cystitis is a chronic condition characterized by pelvic pain, pressure or discomfort related to the bladder.[1] The etiology is still debatable and there is no standard treatment.[2,3] Therefore, the management of BPS/IC is essentially directed to symptom palliation, specifically to pain relief. This symptom is believed to drive other lower urinary tract symptoms generally associated with BPS/IC like frequency and nocturia.[1,4]

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Onabotulinum toxin type A has analgesic properties,[5,6] presumably due to impaired neurotransmitter release from nociceptive neurons at the peripheral and spinal cord endings.[7,8] Accordingly several studies have shown that OnabotA injection in the bladder wall can decrease pain intensity in patients with BPS/IC refractory to standard treatment.[9–11] Frequency and nocturia also often improve. However, it is unclear if the analgesic properties persist unchanged after repeated injections of OnabotA and if intervals between injections remain stable. Nevertheless, this is an essential step before validating OnabotA as a treatment option for symptomatic relief in patients with BPS/IC, despite the fact that the toxin is not approved by the European Medicines Agency[3] or Food and Drug Administration[4] for this condition.

In a previous study we demonstrated that 100 U OnabotA injections in the bladder trigone were highly effective in improving bladder pain, frequency and nocturia in patients with BPS/IC[11] as most nociceptive bladder fibers are concentrated in this region.[12] We previously reported that a second injection was still effective. In this study we increase the number of patients and the number of reinjections to confirm the long-term efficacy and safety of this treatment.

MATERIALS AND METHODS

From a group of 34 patients with BPS/IC refractory to standard management under treatment with OnabotA, 16 women had already received 4 intratrigonal injections. These patients, the first in the cohort to receive this treatment, gave written informed consent. The ethics committee of our institution approved this treatment for patients with BPS/IC refractory to standard management. Patients were informed about possible complications of OnabotA administration including the need for transient self-catheterization.

All patients had symptoms for more than 6 months, and had undergone cystoscopy with hydrodistention and bladder biopsy under general anesthesia. Previous unsuccessful treatments for at least a 6-month trial included oral pentosan polysulfate, amitriptyline, intravesical heparinoids and intravesical dimethyl sulfoxide. Two patients received intravesical resiniferatoxin 2 years before the first OnabotA injection. Pregnancy, neurological diseases, UTIs, aminoglycoside use, bladder outlet obstruction, detrusor overactivity, urinary incontinence, bladder stones, diabetes, hyperthyroidism/hypothyroidism, hypertension and previous pelvic radiotherapy had been excluded in these patients.

The therapeutic effect was evaluated with a 10-point VAS, a 3-day FVC and the O'Leary-Sant score for symptoms and problems before treatment, at the first month and every 3 months after each injection. To increase adherence, the voided volume was measured in only 1 of the 3 days of the FVC. QoL was based on question 8 from the International Prostate Symptom Score, graded from 1 to 6.

Voiding dysfunction and UTIs were assessed 2 weeks after each treatment and every 3 months afterward with ultrasound of the upper and lower urinary tract, urinalysis and urine culture. The duration of each injection was determined when patients requested another treatment.

With the patient under general anesthesia, OnabotA (Allergan, Irvine, California) was injected through a 23 gauge needle (Coloplast A/S, Humlebaek, Denmark) inserted into the trigonal wall under cystoscopic control. A total of 100 U was distributed in 10 sites (10 U/1 ml saline) as described elsewhere.[11] Patients received 500 mg prophylactic ciprofloxacin twice daily for 3 days.

Two weeks after each injection patients were reassessed for post-void residual and muscle weakness. Urine was also collected for culture. Patients were further evaluated by VAS for pain, OSS, 3-day FVC and QoL at the first month and every 3 months thereafter as performed at baseline. Patients could ask for re-treatment after the third month visit if they reported symptom deterioration confirmed by the VAS, OSS, FVC and QoL obtained at that visit.

Results are presented as mean ± SD. A paired t test was used for intragroup comparisons. An ANOVA test was used to determine the variance between treatments. Kaplan-Meier plots were applied to duration of treatments and compared using the log rank test. A p value less than 0.05 was considered statistically significant. Analysis of the data was performed using IBM SPSS® for Mac OS, version 20.0.

RESULTS

Patients had a mean age of 41.8 ± 12.5 years. All patients had typical cystoscopic or histological findings. BPS/IC ESSIC (European Society for the Study of Interstitial Cystitis) classification was 2a (1), 2b (2), 2c (5), 3a (1), 3b (2) and 3c (5) (table 1). Symptoms were present for a mean of 4 ± 2 years. Mean values at baseline were pain score 5.9 ± 0.8 and OSS 28.8 ± 6.3. All patients reported subjective improvement after each of the 4 treatments. One month after the first treatment the pain score decreased to 2.7 ± 0.7 ($p < 0.05$) and OSS decreased to 16.1 ± 3.2 ($p < 0.05$). At 3 months these parameters were still below baseline. At 6 months pain score and OSS were only numerically inferior to baseline. At 9 months the pain score and OSS were similar to baseline (figs. 1 and 2). After OnabotA injections 2, 3 and 4, symptom changes followed the same pattern

Table 1. *Classification of patients according to ESSIC criteria*[1]

Cystoscopy with Hydrodistention	No. Biopsy X (Not done)	No. Biopsy A (normal)	No. Biopsy B (inconclusive)	No. Biopsy C (pos)
X (Not done)	0	0	0	0
1 (normal)	0	0	0	0
2 (glomerulations)	0	1	2	5
3 (Hunner's lesion)	0	1	2	5