Table 3. Comprehensive Summary Table on Literature Review of Onabotulinum Toxin A

Name	Study Design	Methods	Recruitment Criteria	Sample Size	Efficacy Assesment (Outcome) Measure	Findings
Akiyama Y (2015) Japan	Single-center, prospective, open labeled, randomized comparitive study	Single-center, prospective, open labeled, randomized comparitive study. Patients with refactory IC were randomly divided into two groups: immediate injection (group A) or 1-month delayed injection (group B) of botox after allocation. The rate of treatment response (global response assessment ≥+1: slightly improved), and changes in symptom scores and frequency volume chart variables were compared between groups 1 month after allocation. Using subjects of both groups as a single cohort, predictive factors for treatment response at 1 month post-injection and the duration of response were explored.	Between September 2010 and February 2012, 40 IC patients who had received hydrodistention at least once and medical treatment of one or more oral drugs or intravesical agents, yet remained to be symptomatic, six points or higher for the ICPI and ICSI and four points or higher for VAS for pain. Diagnosis for IC was made according to clinical guidelines for IC and hypersensitive bladder syndrome according to the NIDDK.	Full analysis carried out using 34 patients (26 women, 8 men).	Primary end point - response rate between two groups evaluated by GRA a onth after allocation. Patients who rated the efficacy as better than +1 in GRA in the seven-point scale, meaning "slightly improved" "improved" or "remarkably improved" were considered responders in treatment. Secondary end-points were symptom changes from baseline compared a month after allocation by OSSI/OSPI, VAS for pain, QOL based on the QOL index of the International Prostate Symptom Score, the Overactive Bladder Symptom Score, and the frequency volume chart.	All the symptom scores and QOL index significantly improved in group A compared with group B, whereas none of the FVC variables showed significant changes. All symptomatic parameters, except nocturia, significantly improved after BoNT-A treatment. ICPI - p <0.001, ICSI - p <0.001, VAS - p<0.001, OABSS - p<0.001, IPSS - p<0.01, QOL - p <0.001, Daytime frequency (times) - p<0.01, Nocturia - p: 0.17, Average voided volume - p: 0.04, Maximum voided volume - p: 0.01 Additionally, univariate analysis showed that exposure to past HD more than three times and disease duration longer than 6 years were significant factors or better response.
Manning J (2013) Australia	Multicenter, prospective, randomized double blind study	Double-blind study of 54 women with severe, refractory IC from three referral centers whom were randomly allocated to treatment with hydrodistention + injection of normal saline or to hydrodistension + injection of AboBTXA. The O'Leary Sant questionnaires, and bladder diary data were compared between AboBTXA and control patients at baseline, and at 3 months of follow-up. Patients with no improvement after initial treatment had access at minimum of 3 months after initial to AboBTXA if they wished. Patients and doctors remained blinded to the initial treatment. Measurements were made beyond 3 months, but no further randomised comparison was possible due to ability of nonresponsive patients in either group to have AboBTXA treatment.	From January 2004 until Feb 2009, 54 female patients with longstanding refractory IC/BPS were recruited from urogynaecology clinics at three centers. All study participants met NIDDK criteria, with majority having had multiple prior therapies. Being refractory was defined as having failed two or more recognized treatments. Study participants were >18 years of age.	54 female patients	Primary outcome measure: OLS (OLS - SI, OLS - PI) Secondary outcome measures were frequencyand nocturia as measured by bladder diary, and complications such as voiding difficulty.	OLS-PI showed significantly greater improvement at 3 months in the AboBTXA group (p = 0.04). No significant improvement in OLS-SI or total OLS scores between baseline and 3 months for AboBTXA and control groups. 12 patients had proven UTI detected and treated at some time after cytoscopy and injection which was noted to be a confounding factor. Once the analysis was performed without UTI patients, there was an overall improvement in AboBTXA group in all measurements, including total OLS score (p = 0.02), OLS-SI (p = 0.008, OLS - PI (p=0.08) and question 4 of the OLS-PI addressing the problem of bladder pain (p=0.02) There was no significant difference in control or treatment group in number of patients requesting the AboBTXA treatment after 3 months (p = 0.16)
Kuo HC (2013) Taiwan	Prospective interventional study	Thirty-one consecutive patients with IC/BPS who had failed conventional treatments were prospectively enrolled in this study from January 2006 to January 2010. Patients were requested to keep a bladder diary to asses frequency and nocturia. Baseline scores were assessed for O'Leary Sant questionnaires and the VAS responses. Video-urodynamic studies and pottasium chloride sensitivity tests were preformed. Patients with GRA >2 result after treatment were considered to have a successful treatment outcome. Patients were admitted to the hospital for treatment where they received intravesical injection of botox, followed by cytoscopic hydrodistention. After BoNT-A injections, a catheter remained for 1 day and patients were discharged on the next day. Oral antibiotics were prescribed for 7 days. Patients were monitered in the outpatient clinic 2 weeks later. During each follow-up visit, data from each of the GRA, diary, OSS, ICPI, ICSI, Pain VAS were recored. Repeat injections were repeated 6 months after the first treatment, and patients were followed up in the same way. The BoNT-A injection was repeated every 6 months for four times.	Diagnosis of IC/BPS was established based on characteristic symptoms and cytoscopic findings. All patients had been treated with at least 2 of the following medications: oral pentosanpolysulphate or tricyclic antidepressant, intravesical instillations of heparin or hyaluronic acid for more than 1 year - but symptoms remained unchanged.	31 patients (27 female and 4 male)	Primary end point - Global Response assesment (GRA) at 6 months after the fourth BoNT-A injection. Secondary outcome measures were ICSI, ICPI, OSS< VAS, FBC, Frequency, Nocturia, PVR, CBC, FBC, Qmas, Volume	At 6 months after the fourth BoNT-A injection, 19 of 31 patients (61%) had GRA >2 and 12 had a GRA <2. In the patients with GRA >2, OSS< ICSI, ICPI, VAS, FBC, frequency, CBC, and glomerulation grade all showed significant improvement. However, no significant change in measured parameters was noted in patients with GRA <2. Compared with the changes in all measured parameters from baseline to end-point, patients with GRA>2 had significantly greater changes in OSS, ICPI, VAS, FBC, and CBC than those with a GRA <2. The theraputing effects of OSS, VAS, and glomerulation grade were significantly different after the second injection between patients with GRA >2 and GRA <2. Among the patients who were not satisfied with repeated BoNT-A injection, 5 women were found to have Hunner's ulcer. GRA (p = 0.000), OSS (p=0.000), VAS (p=0.000), FBC(p=0.000), CBC (p=0.021), PVR (p=0.030) Glomerulation grades (p=0.026) all showed significant improvement after four repeated injections.
Lee CL	Prospective interventional study	44 consecutive patients with IC/BPS who had failed conventional treatments were prospectively enrolled in this study from January 2008 to January 2012. Patients were requested to keep a bladder diary to asses frequency and nocturia. Baseline scores were assessed for O'Leary Sant questionnaires and the VAS responses. Video-urodynamic studies and pottasium chloride sensitivity tests were preformed. Patients with GRA >2 result after treatment were considered to have a successful treatment outcome. Patients were admitted to the hospital for treatment where they received intravesical injection of botox, followed by cytoscopic hydrodistention. After BoNT-A injections, a catheter remained for 1 day and patients were discharged on the next day. Oral antibiotics were prescribed for 7 days. Patients were monitered in the outpatient clinic 2 weeks later. During each follow-up visit, data from each of the GRA, diary, OSS, ICPI, ICSI, Pain VAS were recored. Repeat injections were repeated 6 months after the first treatment, and patients were followed up in the same way. The BoNT-A injection was repeated every 6 months for four times.	44 consecutive patients with IC/BPS who had experienced conventional treatment failure were prospectively enrolled. Diagnosis was stablished based on characteristic symptoms and cytoscopic findings. All patients had been treated with at least 2 of following medications: oral pentosanpolysulphate or a tricyclic antidepressant and intravesical instillations of heparin or hyaluronic acid for more than one year with symptoms remaining unchanged.	Classified as ulcer(n = 10) or non-ulcer (n = 30) - total 40 women	Global response assessment - 6 months after the 4th set of BoNT-A injections OSS score including ICSI and ICPI, VAS Pain score, voiding diary, and urodynamics variables	Patients with non-ulcer IC/BPS and GRA scores >2 had significanty decreased ICSI, ICPI, OSS, Pain VAS, frequency and nocturia episodes, and increased FBC, cystometric bladder capacity. Patients with non-ulcer IC/BPS and GRA <2 also had decreased ICSI, ICPI, OSS, VAS, frequency episodes, and increased FBC and maximal bladder capacity. Patients with non-ulcer IC/BPS and GRA scores >2 had significanty greater improement than those with non-ulcer IC/BPS and GRA scores <2 for ICSI (P=0.007), ICPI (P=0.016) and OSS (P=0.004)

Table 3 Continued

Kuo HC (2012) Taiwan	Prospective interventional study	81 consecutive patients with IC/PBS who failed conventional treatments were prospectively enrolled in this study from July 2006 to August 2010. Patients were requested to keep a bladder diary to asses frequency and nocturia. Baseline scores were assessed for O'Leary Sant questionnaires and the VAS responses. Video-urodynamic studies and pottasium chloride sensitivity tests were preformed. Patients with GRA >2 result after treatment were considered to have a successful treatment outcome. Patients were admitted to the hospital for treatment where they received intravesical injection of botox, followed by cytoscopic hydrodistention. After BoNT-A injections, a catheter remained for 1 day and patients were discharged on the next day. Oral antibiotics were prescribed for 7 days. Patients were monitered in the outpatient clinic 2 weeks later. During each follow-up visit, data from each of the GRA, diary, OSS, ICPI, ICSI, Pain VAS were recored. Repeat injections were repeated 6 months after the first treatment, and patients were followed up in the same way. The BoNT-A injection was repeated every 6 months until patients felt that the treatment was successful up to 4 injections.	81 consecutive patients with IC/BPS who had experienced conventional treatment failure were prospectively enrolled from July 2006 - August 2010. Diagnosis was established based on characteristic symptoms and cytoscopic findings of glomerulations, petechia, mucosal fissue, or ulceration. All patients had been treated with at least one of the following medications: oral pentosanpolysulphate, intravesical instillation of heparin, hyaluronic acid, or icyclic antidepressant for more than one year but the symptoms remained unchanged or had relapsed. They were investigated thoroughly on enrollment.	81 patients (71 women, and 10 men)	OSS, including ICSI and ICPI. VAS. Video-urodynamic studies at baseline and end-point. Cystometric studies. GRA.	OVerall, the GRA and symptom variables showed persistent improvement with each repeated treatment when baeline of each successie treatment was compared with the initial study baseline level. Among 81 patients, 20 received single injections, 19 received 2 injections, 12 received 3 injections and 30 received 4 injections. The mean sd of ICSI, ICPI, total scores, VAS, FBC, and daytime frequency all showed significant improvement after repeated BoNT-A treatment withd ifferent injections. Significantly better success rates were noted in patients who received 4 repeaeted injections (p=0.0242) and 3 injections (P=0.05), compared to those who received a single injection. However, there was no significant difference of long-term success rates among patients who received 2, 3, and 4 injections.
Chung SD (2012) Taiwan	Prospective non-randomized study	67 patients with IC/PBS who had failed conventional treatments were prospectively enrolled from July 2007 to August 2010. atients were requested to keep a bladder diary to asses frequency and nocturia. Baseline scores were assessed for O'Leary Sant questionnaires and the VAS responses. Video-urodynamic studies and pottasium chloride sensitivity tests were preformed. Patients with GRA >2 result after treatment were considered to have a successful treatment outcome. Patients were admitted to the hospital for treatment where they received intravesical injection of botox, followed by cytoscopic hydrodistention. After BoNT-A injections, a catheter remained for 1 day and patients were discharged on the next day. Oral antibiotics were prescribed for 7 days. Patients were monitered in the outpatient clinic 2 weeks later. During each follow-up visit, data from each of the GRA, diary, OSS, ICPI, ICSI, Pain VAS were recored. Followup was recorded at 3 months and at 6 months post injection.	81 consecutive patients with IC/BPS who had experienced conventional treatment failure were prospectively enrolled. Diagnosis was established based on characteristic symptoms and cytoscopic findings of glomerulations, petechia, mucosal fissue, or ulceration. All patients had been treated with at least one of the following medications: oral pentosanpolysulphate, intravesical instillation of heparin, hyaluronic acid, or icyclic antidepressant for more than one year but the symptoms remained unchanged or had relapsed. They were investigated thoroughly on enrollment.	67 patients (60 women and 7 men)	OSS, including ICSI and ICPI. VAS. Video-urodynamic studies at baseline and end-point. Cystometric studies. GRA.	Significant improvement was shown after injection compared to baseline. ICSI (p=0.000), ICPI (p-0.000), VAS(p=0.000), functional bladder capacity (p=0.000), GRA (p=0.000)
Giannantoni A (2010) Italy	Prospective, non-randomized study.	Patients received one injection of BoNT/A under cystoscopic guidance. At pre- and 3 months post treatment, all patients underwent an urological assessment (voiding diary, urodynamics), a pain quanitification on VAS, and evaluation with the Hamilton Anxiety and Hamilty Depression rating scale, and the QoL form.	Refractory pain in the bladder and urethra, vagina, or prineum during bladder filling or after micturition; frequency, urgency and nocturia; sterile urine, failure of all previous treatments including oral and intravesical therapies.	12 patients (all women)	VAS, QoL, HAM-A, HAM-D, Bladder Diary	Mean VAS score, mean daytime and nighttime urinary frequency all decreased significantly (p<.01, p<.01, p<.01). All domains in QoL and HAM-A significantly improved (p<.01, p<.01). All domains except weight and sleep disoreders significantly improved in HAM-D (p<.01)
Giannantoni A (2008) Italy	Prospective, longitudinal study	Under short general anesthesia, patients were given injections submucosally in the bladder trigone and lateral walls under cystoscopic guidance. A voiding chart and the visual analog scale for pain were used, and urodynamics were performed before treatment and 1,3,5, and 12 months later.	Patients with refractory pain in the bladder and urethra, vagina or perineum durig bladder filling or after micturition who also complained of frequency, urgency, and nocturia. All previous treaments, including oral and intravesical therapies, had failed in all patients.	12 females and 3 males	Clinical Evaluation, VAS, Cystoscopy and urodynamics. Local and/or systemic side effects were noted.	Significant improvements in daytime and night time frequency (p<.01, p<.05) VAS (p<.01), urodynamic parameters (p<.01), and mean maximum cystometric capacity (p<.01) at 1 month and at 3 month. Bladder pain recurred in 11 cases, and mean VAS score increased. At 1 year - bladder pain recurred in all cases. Clinical and urodynamic parameters did not differ with respect to those at baseline. Overall, the study shows significant pain relief at 3 months in 86% of patients. The beneficial effect lasted 5 months in about 30% of cases, but the 1-year follow-up, pain had recurred in all.
Smith CP (2004) United States/Poland	Prospective interventional study	Patients with IC under short general anesthesia or sedation were injected with Botulinum toxin through a cytoscope submucosally in the trigone floor of the bladder. Patients were evaluated with the O'Leary-Sant validated IC questionnaire or with voiding charts and a visual analog pain scale 1 month postoperatively and at subsequent 3 month intervals. Polish patients also underwent pretreatment and post-treatment urodynamic evaluations	IC was diagnosed according to the NIDDK. Previous treatment modalities, including oral and intravesical treatments had failed.	12 females - 6 in US, 6 i	ICSI and ICPI, VAS Urodynamic parameters were assessed in polish patients	Overall, 9 (69%) of 13 patients noted subjective improvement after BTX-A treatment. The ICSI and ICPI mean scores improved by 71% and 69% respectively (p<.05, p<.05). Daytime frequency, nocturia, and pain by VAS decreased by 44$, 45% and 79% (P<0.01). The first desire to void and maximal cystometric capacity increased by 58% and 57% respectively (p<0.01).