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Committee on Gynecologic Practice American Urogynecologic Society

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OnabotulinumtoxinA and the Bladder

ABSTRACT: In January 2013, the U.S. Food and Drug Administration approved the use of onabotulinumtoxinA (also known as Botox A) for the treatment of overactive bladder, thus providing another treatment option for women. Symptoms of overactive bladder have been shown to significantly improve after onabotulinumtoxinA injections compared with no intervention, placebo, pharmacological treatments, and bladder instillation technique. Before considering medical or surgical treatment, all patients in whom overactive bladder is diagnosed should receive instruction in behavioral techniques (eg, bladder retraining drills and timed voids), fluid management, or pelvic muscle exercises with or without physical therapy. Intradetrusor onabotulinumtoxinA may be a second-line treatment option for overactive bladder in appropriate patients, and consideration of its use requires shared decision making between the patient and health care provider. Patients who are candidates for onabotulinumtoxinA injections into the bladder should be counseled about its risks and possible postprocedure adverse events, including the risk of postprocedure urinary retention, urinary tract infections, hematuria, pain, and transient body weakness. Health care providers who perform onabotulinumtoxinA injections must have appropriate training and experience in treating women with pelvic floor disorders, operative cystoscopy privileges, and the ability to diagnose and manage any adverse outcomes after onabotulinumtoxinA injections into the bladder.

The U.S. Food and Drug Administration (FDA) approved onabotulinumtoxinA (also known as Botox A) for cosmetic use in 1991. It has since been FDA-approved for treatment of blepharospasm, strabismus, cervical neck dystonia, hyperhidrosis, chronic migraine, and upper limb spasticity. In August 2011, onabotulinumtoxinA was approved for the treatment of neurogenic bladder; in January 2013, it was approved for treatment of overactive bladder. *Overactive bladder*, a term initially introduced by the pharmaceutical industry, is defined as urinary urgency, typically accompanied by frequency and nocturia, with and without urge urinary incontinence in the absence of urinary tract infection or other obvious pathology (1). The term overactive bladder includes the previously defined term of “detrusor overactivity” (idiopathic) (2). This joint Committee Opinion of the American College of Obstetricians and Gynecologists and the American Urogynecologic Society will focus on the use of onabotulinumtoxinA for the treatment of overactive bladder.

Botulinum toxin, a potent neurotoxin derived from the anaerobic bacterium *Clostridium botulinum*, acts primarily as a muscle paralytic by inhibiting the presynaptic release of acetylcholine from motor neurons at the neuromuscular junction. Botulinum toxin also has effects on the afferent side of the nervous system by decreasing the sensory response of the C afferent fibers. There are several subtypes of botulinum toxin, but the most commonly used is subtype A. OnabotulinumtoxinA is administered by cystoscopic injection of multiple aliquots into the detrusor muscle. The FDA-approved dosage for the treatment of neurogenic bladder is 200 units; the FDA-approved dose for overactive bladder is 100 units.

Efficacy

An extensive Cochrane review (3) has summarized the literature for the use of botulinum toxin for overactive bladder. Symptoms of overactive bladder have been shown to significantly improve after botulinum toxin injections even at 12 months ($P<.001$) compared with

no intervention, placebo, pharmacological treatments, and bladder instillation technique. This review also summarized results of different types, doses, and injection techniques of botulinum toxin.

A multi-institutional, randomized, double-blind, placebo controlled trial compared 200 units of onabotulinumtoxinA with placebo for neurologically normal women who were refractory to two first-line treatments (4). The trial demonstrated that 60% of the women who received onabotulinumtoxinA had a clinical response based on the Patient Global Impression of Improvement index. Even though this study was halted before completion because of concerns with elevated postvoid residual volumes, onabotulinumtoxinA revealed a statistically significant improvement over placebo.

The Anticholinergic vs OnabotulinumtoxinA Comparison study was a multicenter randomized trial that compared the effectiveness of 6 months of daily anticholinergic therapy with a single intradetrusor injection of 100 units of onabotulinumtoxinA in patients with overactive bladder symptoms (5). The study included participants who had never taken anticholinergic medications and those who had taken two or fewer prior anticholinergic medications. Results demonstrated that anticholinergics had similar rates of improvement in symptoms of overactive bladder compared with onabotulinumtoxinA injections. However, patients who underwent onabotulinumtoxinA injections had significantly higher cure rates compared with patients who received anticholinergic medication. Risk of voiding dysfunction that required catheterization and urinary tract infection in women who received onabotulinumtoxinA injection was 5% and 33%, respectively.

Evaluation

The diagnosis of overactive bladder should be confirmed by appropriate evaluation. (See Practice Bulletin No. 63 *Urinary Incontinence in Women*, for information on evaluation of urinary incontinence [2].) A differential diagnosis for overactive bladder may include other disorders such as recurrent urinary tract infections, interstitial cystitis or painful bladder syndrome, hematuria, and pelvic organ prolapse.

Technique of Injection

The technique of mixing the onabotulinumtoxinA and how to inject it can be found on the package insert (6). OnabotulinumtoxinA injection is most often performed as a cystoscopic office procedure under local anesthesia; however, in certain circumstances, such as patient discomfort or lack of office-based equipment, the injection may be performed in an operating room as an outpatient procedure.

When performed in an office setting, a local anesthetic is instilled into the bladder 30 minutes before injection. Cystoscopy may be performed using either a 30-degree lens or with an injection cystoscope or flexible

cystoscope with injection needle. Injections are spread out over different rows to equally cover the bladder dome and posterior base, sparing the trigone and ureteral orifices (see Fig. 1).

The patient should be observed until a spontaneous void occurs. If the patient is unable to void or demonstrates inadequate voiding, she should be instructed on self-catheterization. See “Postprocedure Recommendations” for additional information.

Candidates for OnabotulinumtoxinA Bladder Injections

Before considering medical or surgical treatment, all patients in whom overactive bladder is diagnosed should receive instruction in behavioral techniques (eg, bladder retraining drills and timed voids), fluid management, or pelvic muscle exercises with or without physical therapy. A recent randomized controlled trial indicated that onabotulinumtoxinA may be considered a second-line treatment (5). Shared decision making between the patient and health care provider should include a discussion about where onabotulinumtoxinA injections ultimately fit in the treatment algorithm depending upon symptom severity, bother, presence of other co-morbidities, and risk–benefit ratio for the patient.

Contraindications to onabotulinumtoxinA usage ascertained from the medical history include a known hypersensitivity to onabotulinumtoxinA, dysphagia, pre-existing neuromuscular disorders (myasthenia gravis), and compromised respiratory status. OnabotulinumtoxinA is considered an FDA Pregnancy Category C drug, so there are no adequate and well-controlled studies in pregnant

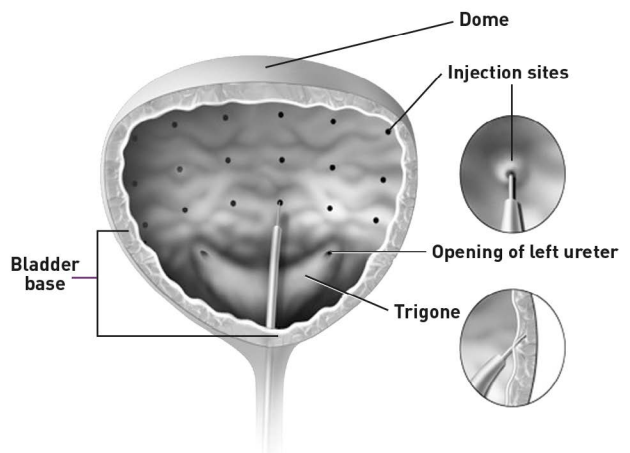


Fig. 1. Pattern for intradetrusor onabotulinumtoxinA injections for the treatment of overactive bladder or detrusor overactivity associated with a neurologic condition. (Reprinted from Allergan I. Botox: highlights of prescribing information. Irvine (CA): Allergan; 2013. Available at: http://www.allergan.com/assets/pdf/botox_pi.pdf. Retrieved December 18, 2013.) ←

women. Caution should be used for women who are breastfeeding.

Patient Counseling

Patients who are candidates for onabotulinumtoxinA injections into the bladder should be counseled about its risks and possible postprocedure adverse events, including the risk of postprocedure urinary retention, urinary tract infections, hematuria, pain, and transient body weakness. Patients who are considering onabotulinumtoxinA injections should be counseled about the risk of postprocedure urinary retention or incomplete bladder emptying that may require clean intermittent self-catheterization or catheter placement (5). Patients also should be counseled that the effect of onabotulinumtoxinA is transient and can wear off in 6–15 months; reinjections may be needed for continued effectiveness. The manufacturing label states that patients should be considered for reinjection when the clinical effect of the previous injection has diminished, but no sooner than 12 weeks from the prior bladder injection (6).

Postprocedure Recommendations

There are currently no evidence-based recommendations on when to follow up with patients who have received onabotulinumtoxinA injections. Based upon expert opinion, patients should be contacted 3–7 days postprocedure to assess the effectiveness of the injection and assess bladder emptying. If symptoms cannot be assessed over the telephone, patients should be seen in the office. Because incomplete bladder emptying can occur after the onabotulinumtoxinA injection, and some patients may report minimal voiding, many experts recommend an in-office assessment of postvoid residual urine volume by catheterization or bladder ultrasonography postprocedure or when an assessment of bladder emptying is indicated. Clean intermittent self-catheterization may be recommended for postvoid residual volumes greater than 300 mL or greater than 150 mL in the presence of bothersome retention symptoms (5). For those patients sent home who require clean intermittent self-catheterization, a clear follow-up plan should be outlined, including how often to use the catheter and at what volumes catheterization should be continued or discontinued. Urinalysis and urine culture also may be indicated.

Clinician Training and Experience

Health care providers who perform onabotulinumtoxinA injections must have appropriate training and experience in treating women with pelvic floor disorders, operative cystoscopy privileges, and the ability to diagnose and manage any adverse outcomes after onabotulinumtoxinA injections into the bladder. For example, subspecialists in female pelvic medicine and reconstructive surgery and urologists are qualified to inject onabotulinumtoxinA for overactive bladder.

Summary and Recommendations

The January 2013 FDA approval of onabotulinumtoxinA for the treatment of overactive bladder provides another treatment option for women. Where onabotulinumtoxinA bladder injections fit into a health care provider's treatment algorithm is dependent on an assessment of each patient's symptom severity and bother, the effect of incontinence on daily activities, previous treatment history, an assessment of the risk–benefit ratio for the patient, and the health care provider's capacity to manage postprocedure adverse events. Based on available data and expert opinion, the American College of Obstetricians and Gynecologists and the American Urogynecologic Society make the following recommendations:

- The diagnosis of overactive bladder should be confirmed by appropriate evaluation.
- Intradetrusor onabotulinumtoxinA may be a second-line treatment option for overactive bladder in appropriate patients, and consideration of its use requires shared decision making between the patient and health care provider. Patients should be counseled about risks and possible postprocedure adverse events of onabotulinumtoxinA injections, including urinary retention, incomplete bladder emptying, and urinary tract infections.
- Health care providers who perform onabotulinumtoxinA injections as a treatment option must have appropriate training and experience in treating women with pelvic floor disorders, operative cystoscopy privileges, and the ability to diagnose and manage any adverse outcomes after onabotulinumtoxinA injections into the bladder.

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