Onabotulinumtoxin - A Injections for the Treatment of Neurogenic Detrusor Overactivity

Raluca Borcăiaș[1], S. Rașcu[1,2], V. Jinga[1,2], D. Mischianu[1,3], A. Manu-Marin[4]

[1] *"Carol Davila" University of Medicine and Pharmacy*

[2] *"Prof. Dr. Th. Burghele" Clinical Hospital, Urology Department*

[3] *"Dr. Carol Davila" Central Military Clinical Emergency University Hospital, Urology Department*

[4] *Evomed Clinic*

Abstract

Introduction and Objectives. The neurogenic detrusor overactivity (NDO) represents the pathology in which the bladder detrusor overactivity can be caused by a series of neurological conditions. The burden of NDO is not all neglectable, impairing the patients' quality of life. Currently there is no optimal medical therapy to relieve all the neuro-urological symptoms available. Even if antimuscarinic agents have been used for many years with good clinical and urodynamic response, there is still limited data for tailoring the perfect antimuscarinic treatment for individual patients with NDO. High doses or combination of anticholinergics are recommended for maximizing the outcome in neurological patients, still, the incidence of adverse events is the major factor for therapy discontinuation. For patients who abort anticholinergic drugs or for unresponsive patients or for patients unwilling to assume the side effects, other types of treatments should be regarded. In recent years, Onabotulinumtoxin A has emerged as the most effective minimally invasive treatment to reduce NDO, therefore an efficient treatment alternative.

Materials and Methods. The aim of this prospective study performed on 15 patients was to assess the efficacy of botulinum toxin A intradetrusor injections for the treatment of NDO. Intradetrusor injections with Onabotulinumtoxin A 200 U were performed through a minimally invasive flexible cystoscopy technique, under general intravenous anesthesia. Urodynamic studies were performed at baseline and 3 months after injecting the botulinum toxin. Urodynamic parameters like reflex volume (RV), maximum cystometric capacity (MCC) and maximum detrusor pressure (MDP) were assessed. The number of incontinence episodes and the score of quality of life questionnaires were also analyzed at baseline and 3 months after the injection.

Results. Mean age for the study group was 48,73 years old, most of the patients presented with spinal cord injury or multiple sclerosis. RV increased in most of the cases with an average of 49.26 ml (42.84%). MCC presented an overall average increase of 69.93 ml (57.32%). MDP showed an average decrease of 12.15 cm H_2O, accounting for 22.93%. Incontinence episodes were reduced with 66.66% compared to baseline. On the Overactive Bladder Perception Score an average decrease of 0.73 (12.5%) was recorded, while on The VAS QoL an average decrease of 1.93 points (22.52%) was noted. No major adverse events were recorded.

Conclusions. Botulinum toxin A intradetrusor injection can be a feasible minimally invasive treatment for patients with neurogenic detrusor overactivity not only for patients who are non-responsive or who fail to tolerate anticholinergic medication, with possible low rates of adverse events that lead to discontinuation.

Key-words: maximum cystometric capacity, maximum detrusor pressure, neurogenic detrusor overactivity, Onabotulinumtoxin A, quality of life, reflex volume, urinary incontinence.

Correspondence to: Dr. Stefan Rascu M.D.
"Prof. Dr. Th. Burghele" Clinical Hospital, Urology Department
20 Panduri Str., District 5, code 050659, Bucharest, Romania
Tel: +40214106910
e-mail: stefanrascu.sr@gmail.com

Introduction and Objectives

Ever since the International Continence Society (ICS) has standardized the definitions of the lower urinary tract dysfunctions in 2002, the overactive bladder (OAB) represents a symptom syndrome characterized by urgency with or without urinary incontinence, associated with increased urinary frequency and nocturia. If OAB appears in the setting of a neurologic pathology, it is classified as neurogenic OAB, otherwise, if no evidence of an underlying neurologic disorder exists, OAB is classified as idiopathic. While OAB is a clinical diagnosis, the detrusor overactivity (DO) is a paraclinical finding at the urodynamic testing, where the involuntary contractions of the detrusor appear usually during the filling phase of the bladder. Consequently, DO is usually classified as neurogenic – NDO or idiopathic – IDO [1]. NDO can be caused by a series of neurological conditions such as Parkinson's disease (PD), spinal cord injury (SCI), multiple sclerosis (MS), spina bifida (SB), strokes or even Alzheimer's disease. The burden of NDO is not all neglectable. MS is estimated to have a median worldwide incidence of 2.5/100000 and a median prevalence 30/100000. 65% of the MS patients show signs of NDO, 51-80% of them report bladder dysfunction and half of them present with urinary incontinence caused by urgency. SCI acknowledged an estimated incidence of 16/1000000 in Europe. About 80% of the SCI patients develop neurogenic lower urinary tract dysfunction, the prevalence of urge urinary incontinence being of about 50% [2, 3]. It is a very well-known fact that OAB significantly impairs the patients' quality of life (QoL) and that, furthermore, patients with NDO are even more disadvantaged by their neurologic deficits. Moreover, the neurogenic bladder dysfunction can lead to renal failure by compromising the storage function of the bladder [4]. The upper urinary tract is at risk especially in patients who suffer from high pressure in their detrusor muscle during the filing phase. In patients who suffer from spinal cord injury and/or spina bifida, the risk of developing renal insufficiency is substantially higher compared to patients who present with non-traumatic slowly progressive neurological affections, like multiple sclerosis or Parkinson's disease [5, 6]. Renal failure is the next mortality factor for patients with SCI after the trauma itself [7, 8]. In treating patients with NDO, first concern should be to keep the detrusor pressure within safe limits during filling and voiding phase in order to reduce the mortality from urological causes in these patients [9, 10]. For patients who develop high detrusor pressure during the filling phase, meaning DO and low bladder compliance, the treatment should focus on the conversion of an overactive high-pressure bladder into a low-pressure one, not taking into consideration the resulting residual urine. Reduction of the detrusor pressure will contribute to improving the urinary continence, therefore improving the patients' QoL. It will also help preventing urinary tract infections [11, 12]. The urological treatment for these NDO patients should have the following goals – protecting the upper urinary tract, achieving urinary continence, restoring the lower urinary tract function and improving the patients' QoL, as primary goals and taking into consideration the patients' disability and risk of complications, as secondary goal [11, 13].

In terms of treatment, currently there is no optimal medical therapy to relieve all the neuro-urological symptoms available. Most of the times, intermittent catheterization together with the administration of antimuscarinic agents is the combination of choice in preventing urinary tract damage and improving long-term outcomes, especially in SCI or MS patients [14, 15]. In 2017, the European Association of Urology still recommends in its guidelines the administration of antimuscarinics as first line medical treatment for NDO patients, due to their effect on increasing bladder capacity and reducing the episodes of urinary incontinence. Even if this line of treatment is used for many years and the clinical and urodynamic responses are well documented compared to placebo in a series of clinical trials, there is still limited data for tailoring the antimuscarinic treatment for individual patients with NDO due to SCI. High doses or combination of anticholinergics are recommended for maximizing the outcome in neurological patients, still, the incidence of adverse events is the major factor for therapy discontinuation [16, 17]. For patients who discontinue or do not tolerate anticholinergic drugs due to their adverse events or for those who are unresponsive to this type of treatment, other types of treatments should be regarded. After its FDA (Food and Drug Administration) approval back in 2011, the use of onabotulinum toxin A has emerged as an efficient alternative for the treatment of NDO patients. The intradetrusor injections with botulinum toxin A cause a reversible, long-lasting, chemical denervation for up to nine months. Furthermore, botulinum toxin A has proven its efficacy for patients with NDO due to MS or SCI in two phase III randomized controlled trials [19, 20] and reinjections are allowed without loss of efficacy. The most frequent side effects are urinary tract infections and an increase of the postvoid residue, therefore intermittent catheterisation may become necessary. The severe adverse events are very rare,

consisting mainly of respiratory problems or generalized muscular weakness [19, 20, 21]. In 2017, the European Association of Urology recommend, with a level of evidence of "1a" and an "A" grade of recommendation, the Botulinum toxin intradetrusor injection as the most effective minimally invasive treatment to reduce NDO in SCI or MS patients [16].

Materials And Methods

The aim of this prospective study we have performed on 15 patients was to assess the efficacy of botulinum toxin A intradetrusor injections for the treatment of NDO. Patients with detrusor overactivity diagnosed in the urodynamic study and with an underlying already diagnosed neurologic condition, mainly SCI and MS, were included in the study. The exclusion criteria were represented by the presence of positive urine culture, the presence of urinary lithiasis, the personal history of interstitial cystitis or urothelial tumors, and the use of oral anticoagulant therapy. At baseline, after the pre-study work-up, patients completed a bladder diary and a standardized quality of life questionnaire. After signing the informed consent, patients received intradetrusor injections with Onabotulinumtoxin A 200 U dissolved in 30 ml NaCl solution, in 30 sites across the bladder, sparing the bladder trigone, through a minimally invasive flexible cystoscopy technique, under general intravenous anesthesia. Urodynamic studies were performed at baseline and 3 months after injecting the botulinum toxin. Adverse events were also monitored. Urodynamic parameters like reflex volume (RV), maximum cystometric capacity (MCC) and maximum detrusor pressure (MDP) were assessed. The number of incontinence episodes and the score of quality of life questionnaires were also analyzed at 3 months following the injection.

Results

The mean age of the study group was 48.73 years old, ranging from 28 to 67 years old. Most of the patients presented with SCI – seven patients, four patients with MS, one patient with arterio-venous medullar fistula, one patient with Lyme disease, one patient with congenital myelomeningocele and one patient with lumbar disc hernia. Three months after injecting the Onabotulinumtoxin A, the urodynamic parameters like RV, MCC, MDP were re-assessed and, in most cases they were importantly improved. These parameters and their evolution are illustrated in the following table:

Reflex volume (RV) (ml)			Maxium Cystometric Capacity (MCC) (ml)			Maximum detrusor pressure (MDP) (cm H2O)		
Baseline	3 months	Δ	Baseline	3 months	Δ	Baseline	3 months	Δ
115	214	+ 99	164	451	+ 287	44	38	- 6
170	185	+ 15	202	246	+ 44	95	70	- 25
74	206	+ 132	91	335	+ 244	54	25	- 29
210	314	+ 104	225	319	+ 94	23	16	- 7
180	163	- 17	197	185	- 12	53	96	+ 43
190	115	- 75	224	148	- 76	32	23	- 9
136	112	- 24	197	372	+ 175	27	28	- 1
407	401	- 6	436	401	- 35	33	28	- 5
103	273	+ 170	121	305	+ 184	15	10	- 5
421	434	+ 13	457	475	+ 18	10	9	- 1
170	268	+ 98	379	281	- 98	58	24	- 34
480	482	+ 2	499	510	+ 11	18	4	- 14
306	236	- 70	416	246	- 170	55	49	- 6
128	421	+ 293	325	408	+ 83	14	12	- 2
75	80	+ 5	155	455	+ 300	22	7	- 15

Table 1 – Reflex volume, maximum cystometric capacity and maximum detrusor pressure at baseline and 3 months after injection with the botulinum toxin.

The reflex volume (RV) increased in most of the cases as shown in figure 1. In 10 out of the 15 patients, the reflex volume's increase ranged between 15 and 293 ml, with an average 80.96% improvement, while in the other five patients, the decrease of the RV ranged between 17 and 70 ml, with an average decrease of 33.39%. The average increase for the study group was 49.26 ml with an average increase of 42.84%.

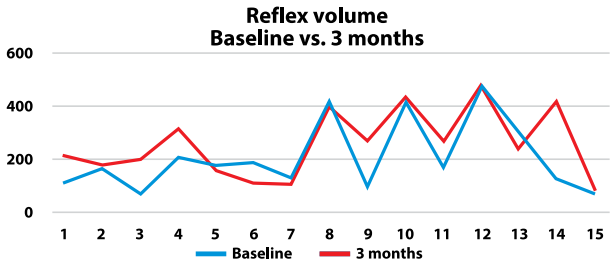

Figure 1 – Reflex volume in the study group at 3 months after injection compared to baseline

The maximum cystometric capacity was observed to increase in 10 patients from our study group, with values ranging from 11 to 300 ml, with an average increase of 144 ml (figure 2), meaning 97.28%. In five of the studied patients, the MCC somehow decreased with 12 to 170 ml, with an average decrease of 78.2 ml, with an average of 22.95%. The overall average increase for the study group was 69.93 ml, representing an average of 57.32%.

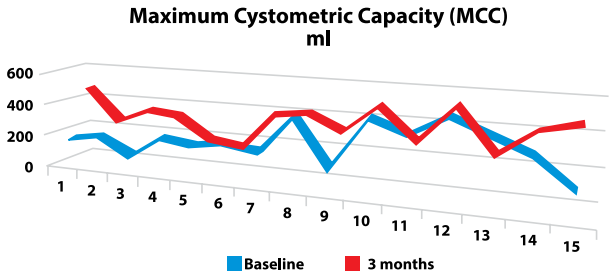

Figure 2 – Maximum cystometric capacity in the study group at 3 months after injection compared to baseline

In what concerns the maximum detrusor pressure measured before and 3 months after the injection with Onabotulinumtoxin A, it can be observed that it was decreased in most of the studied patients. Only in one of the five patients the MDP increased with 43 cm H_2O, representing about 81% out of the baseline MDP. The decrease ranged in the 1 - 34 interval, with an average decrease of 12.15 cm H_2O, representing a 22.93 percent. The global average decrease for the study group was 7.6 cm H_2O, with a mean of 14.33%. The variation in MDP at 3 months compared to baseline is represented in figure 3.

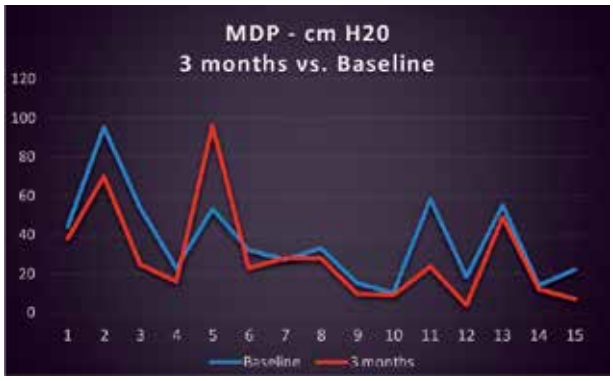

Figure 3 – Maximum detrusor pressure variation in the study group at 3 months after injection compared to baseline

Incontinence episodes were also evaluated at baseline and at 3 months after the injection based on the data recorded in the patients' bladder diary. At baseline, all the patients were having at least 2 incontinence episodes in the last two days, with a maximum of 23. At 3 months, 6 out of the 15 patients declared that they hadn't encountered any incontinence episode in the last 2 days, with an average decrease of 5.33 incontinence episodes, representing a global average decrease of 66.66% in incontinence, compared to baseline. The reduction of the incontinence episodes is represented in the next figure:

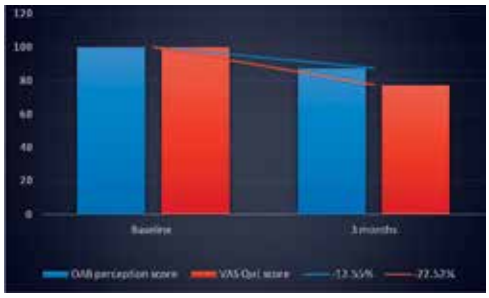

Figure 4 Incontinence episodes at 3 months after injection compared to baseline, according to the bladder diary

The quality of life was also assessed into the study group regarding the incontinence episodes using the Visual Analogue Scale (VAS) on the Quality of Life (QoL) and the Overactive Bladder Perception Score questionnaires, showing an important improvement compared to baseline. On the Overactive Bladder Perception Score an average decrease of 0.73 points was observed, representing an overall 12.5% decrease, on an interval ranging from 0 to 60%, while on The VAS QoL

we have registered an average decrease of 1.93 points, accounting for 22.52% overall decrease (Figure 5).

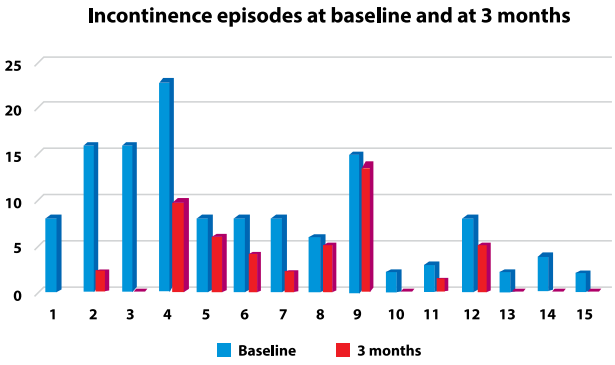

Figure 5 – OAB perception and VAS QoL questionnaires scores variation group at 3 months after injection compared to baseline

Discussions

Madersbacher et al. published in 2013 one of the most extensive reviews of literature regarding the efficacy, tolerability and safety of the oral antimuscarinics administration in adult NDO; the authors presented in this article an increase in the MCC ranging between 21% and 104% compared to baseline and a decrease in the MDP ranging from 33% to 38% [22, 23, 24, 25, 26, 27, 28]. The average increase in the MCC from the above-mentioned review, considering all the analyzed studies, was 63.7%, while the average rate of increase of the MCC analyzing only the placebo controlled clinical trials presented was 59.8% [22, 23, 24, 25]. The average MDP decrease was 36.8% [22 – 28] for all the presented studies and 35.9% for the placebo controlled trials reviewed [22 – 25]. Regarding the reduction in incontinence episodes, it ranged from 13.8% to 38.7%, with an average of 26.25% [22,28]. Unfortunately, there are few studies in the literature that used standardized questionnaires to assess the quality of life, therefore data on this subject is quasi inexistent in this extensive review. In terms of adverse events of oral antimuscarinic medication for treating NDO patients, they ranged between 3 and 78.7% of patients, that actually led to a rate of treatment discontinuation of 5.6 to 23% [22 – 25, 28].

Although not all the patients were perfect responders to injecting 200 U of Onabotulinumtoxin A into the bladder detrusor, the majority showed an improvement of the assessed urodynamic parameters. MCC increased with a global average of 57.32%, while the MDP decreased with an average of 22.93%. The reflex volume was also improved with a global average increase of 42.94. The reduction in incontinence episodes was substantial, with an average decrease of 66.66%, a significantly larger percent if to be compared to the incontinence reduction of the oral antimuscarinic agents [22, 28]. Although not very well assessed in the reviewed literature, the quality of life is nevertheless an important aspect for patients with NDO. We've observed an average decrease of 0.73 points, accounting for an overall average 12.5% decrease, on an interval ranging from 0 to 60%, on the Overactive Bladder Perception Score. On the VAS QoL questionnaire we have registered an average decrease of 1.93 points, accounting for 22.52% overall average decrease compared to baseline. Moreover, we have only observed one adverse event during this phase of our study, when a patient presented a comitial attack, most probably due to the interruption of the antiepileptic medication, which was treated conservatively and resolved, that led to postponing the injection of toxin for 8 days.

Taking all these aspects into account, our study showed promising results in terms of urodynamic parameters improvement, incontinence episodes reduction and quality of life improvement, comparable to the results from the international published literature [29, 30]. Furthermore, the improvement of the urodynamic parameters from our study are relatively close to the ones obtained with antimuscarinic oral medication in NDO patients, from the reviewed literature, possibly with less adverse events and possibly with less chances of discontinuation.

Conclusions

Botulinum toxin A injection in the detrusor muscle can be a feasible minimally invasive treatment for patients with neurogenic detrusor overactivity and not only for patients who are non-responsive or who fail to tolerate anticholinergic medication, with possible lower rate of adverse events that lead to discontinuation. Injections with botulinum toxin type A appeared to be well tolerated and they were correlated to improving patients' incontinence episodes, urodynamic parameters and quality of life at 3 months.

Although it has been approved by several important healthcare authorities for the use in NDO treatment and for reinjection, we feel the need of emphasizing that further studies with high level of evidence will be needed to assess and establish the best guideline recommendations in terms of dosage, injection and reinjection protocols, rate of adverse events and safety profile.

References

1. Abrams P, Cardozo L, Fall M, et al. *The standardisation of terminology of lower urinary tract function: report from the standardisation subcommittee of the International Continence Society.* Neurourol Urodyn 2002;21(2):167–78.
2. Borcăiaș R, Manu-Marin A , Nedelea S, Rascu S, Jinga V. *Use of the botulinum toxin A in the treatment of the neurogenic detrusor overactivity.* Rev Rom Urol 2016; 15(1):11-16.
3. Haab F. *The conditions of neurogenic detrusor overactivity and overactive bladder.* Neurourol Urodyn. 2014 Jul;33 Suppl 3:S2-5.
4. Smaldone MC, Ristau BT, Leng WW. *Botulinum Toxin Therapy for Neurogenic Detrusor Overactivity.* Urol Clin N Am 2010;37(4):567-580.
5. Ouyang L, Bolen J, Valdez R, et al. *Characteristics and survival of patients with end stage renal disease and spina bifida in the United States renal data system.* J Urol 2015;193(2):558-564.
6. Lawrenson R, Wyndaele JJ, Vlachonikolis I, Farmer C, Glickman S. *Renal failure in patients with neurogenic lower urinary tract dysfunction.* Neuroepidemiology 2001;20(2):138-143.
7. Game X, Castel-Lacanal E, Bentaleb Y, et al. *Botulinum toxin A detrusor injections in patients with neurogenic detrusor overactivity significantly decrease the incidence of symptomatic urinary tract infections.* Eur Urol 2008;53(3):613-618.
8. Chamberlain JD, Meier S, Mader L, von Groote PM, Brinkhof MW, et al. *Mortality and longevity after a spinal cord injury: systematic review and meta-analysis.* Neuroepidemiology 2015;44(3):182-198.
9. Thietje R., Pouw MH, Schulz AP, Kienast B, Hirschfeld S. *Mortality in patients with traumatic spinal cord injury: descriptive analysis of 62 deceased subjects.* J Spinal Cord Med 2011; 34(5):482-487.
10. Jamil F. *Towards a catheter free status in neurogenic bladder dysfunction: a review of bladder management options in spinal cord injury (SCI).* Spinal Cord 2001;39(7):355-361.
11. Stöhrer M, Kramer G, Löchner-Ernst D, Goepel M, Noll F, Rübben H. *Diagnosis and treatment of bladder dysfunction in spinal cord injury patients.* Eur Urol Update Series;3(1994):170 – 175.
12. Rodrigues P, Hering F, Campagnari JC. *Involuntary detrusor contraction is a frequent finding in patients with recurrent urinary tract infections.* Urol Int 2014;93(1):67-73.
13. Drake M., et al. *Conservative management in neuropathic urinary incontinence, in Incontinence* - P. Abrams, L. Cardozo, S. Khoury & A. Wein, Editors. Health Publication Plymouth 2013;827-1000.
14. Wyndaele JJ, Kovindha A, Madersbacher H, et al. *Neurologic urinary incontinence.* Neurourol Urodyn. 2010;29(1):159-164.
15. Phé V, Chartier-Kastler E, Panicker JN. *Management of neurogenic bladder in patients with multiple sclerosis.* Nat Rev Urol. 2016;13(5):275-288.
16. Blok B., Pannek J., Castro Diaz D, et al. *Guidelines on Neuro-urology,* European Association of Urology 2017;19-22.
17. Madhuvrata, P., Singh M, Hasafa Z, Abdel-Fatah M. *Anticholinergic drugs for adult neurogenic detrusor overactivity: a systematic review and meta-analysis.* Eur Urol 2012. 62:816-830.
18. Del Popolo G., Filocamo MT, Li Marzi V, et al. *Neurogenic detrusor overactivity treated with english botulinum toxin a: 8-year experience of one single centre.* Eur Urol 2008. 53(5): 1013-1019.
19. Cruz F, Herschorn S, Aliotta P, et al. *Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity, randomized, double blind, placebo-controlled trial.* Eur Urol 2011;60(4):742-50.
20. Schurch B, de Seze M, Denys P, et al. *Botulinum toxin type A is a safe and effective treatment for neurogenic urinary incontinence: results of a single treatment, randomized, placebo controlled 6-month study.* J Urol 2005;174(1):196-200.
21. Ginsberg D, Gousse A, Keppenne V, et al. *Phase 3 Efficacy and Tolerability Study of OnabotulinumtoxinA for Urinary Incotinence From Neurogenic Detrusor Overactivity.* J Urol 2012;187:2131-2139.
22. Madersbacher H, Mürtz G, Stöhrer M. *Neurogenic detrusor overactivity in adults: a review on efficacy, tolerability and safety of oral antimuscarinics.* Spinal Cord 2013; 51:432-441.
23. Stöhrer M, Frohneberg D, Loechner-Ernst D, Sauter P, Mandaika B. *Oxybutynin in the treatment of detrusor hyperreflexia in patients with spinal cord injury: A multicentre randomised double-blind study.* Annual Meeting of the American Spinal Cord Injury Association. Orlando, USA 1990.
24. Stöhrer M, Madersbacher H, Richter R, Wehnert J, Dreikorn K. *Efficacy and safety of propiverine in SCI-patients suffering from detrusor hyperreflexia—a double-blind, placebo-controlled clinical trial.* Spinal Cord 1999; 37:196–200.
25. Stöhrer M, Bauer P, Giannetti BM et al. *Effect of trospium chloride on urodynamic parameters in patients with detrusor hyperreflexia due to spinal cord injuries. A multicentre placebo-controlled double-blind trial.* Urol Int 1991; 47:138–143.
26. Gajewski JB, Awad SA. *Oxybutynin versus propantheline in patients with multiple sclerosis and detrusor hyperreflexia.* J Urol 1986; 135:966–968.
27. Madersbacher H, Stöhrer M, Richter R, Burgdörfer H, Hachen HJ, Mürtz G. *Trospium chloride versus oxybuynin: a randomized, double-blind, multicentre trial in the treatment of detrusor hyperreflexia.* Brit J Urol 1995; 75:452–456.
28. Stöhrer M, Mürtz G, Kramer G, Schnabel F, Arnold EP, Wyndaele JJ. *Propiverine Study Group. Propiverine compared to oxybutynin in neurogenic detrusor overactivity—results of a randomized, double blind, multicenter clinical study.* Eur Urol 2007; 51:235–242.
29. Mangera A, Apostolidis A, Andersson KE, et al. *An updated systematic review and statistical comparison of standardised mean outcomes for the use of botulinum toxin in the management of lower urinary tract disorders.* Eur Urol 2014;65(5):981-990.
30. Mehta S, Hill D, McIntyre A, et al. *Meta-analysis of botulinum toxin A detrusor injections in the treatment of neurogenic detrusor overactivity after spinal cord injury.* Arch Phys Med Rehabil 2013;94(8):1473-1481.