Medical Research Archives

ESMED
European Society of Medicine

OPEN ACCESS

Published: November 30, 2022

Citation: Al-nisr MH and Alguacil NC, 2022. Real Life Experience with Individualized Doses of Incobotulinumtoxina in Patients with Severe Spasticity Due to Acquired Brain Injury, Medical Research Archives, [online] 10(11). https://doi.org/10.18103/mra.v10i11.3342

DOI
https://doi.org/10.18103/mra.v10i11.3342

ISSN: 2375-1924

RESEARCH ARTICLE

Real Life Experience with Individualized Doses of Incobotulinumtoxina in Patients with Severe Spasticity Due to Acquired Brain Injury

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ABSTRACT
The objective of the present study was to evaluate the effectiveness and tolerability of incobotulinumtoxinA, at doses according to individual needs, in 10 patients with acquired brain injury and severe upper and lower limb spasticity. Patients received a multipattern periodic treatment with ultrasound-guided injections of incobotulinumtoxinA at doses of 800-900 U in the upper and lower limbs. The mean number of injection cycles per patient was 4.2. The 0-10 visual analogue scale for pain score decreased significantly from pre-injection (mean: 4.7) to four-week post-injection (mean: 0.7). Similarly, the mean Ashworth Scale score (muscular tone assessment) at four-week post-injection (mean: 1.4) was significantly lower than at injection (mean: 2.5). Except for two patients in one pattern, all cases showed an improvement in passive range of motion assessments using goniometry. All patients reported maximum satisfaction with the treatment, all reporting "much improved" after the treatment. No treatment-related adverse effects were observed during the study. Individualized doses of incobotulinumtoxinA are effective and well-tolerated for this type of patients and allow better management of their severe spasticity. Therefore, individualization of doses should be taken into account for optimizing clinical outcomes and improving the patients' treatment satisfaction.

1. INTRODUCTION

Acquired brain injury (ABI) is a type of traumatic injury caused to the brain that occurs after birth[1]. It can be associated with significant and chronic impairments across multiple areas of functioning, including physical, cognitive, emotional, behavioral, and social domains. Muscle spasticity is one of the main clinical complications following ABI, which may lead to different musculoskeletal issues such as muscle contracture, joint stiffness, reduced range of movement and pain[2]. Spasticity has been associated with the damage of upper motor neurons of the cortico-reticular pathways in the brain cortex or internal capsule or in the reticulospinal or vestibulospinal tracts in the spinal cord[3]. Studies involving different populations (stroke, spinal cord injury and multiple sclerosis) have estimated a prevalence of problematic spasticity in between 30% and 50% of cases with traumatic brain injury[4].

Various therapeutic strategies have been proposed for the treatment of spasticity including surgical, medical and rehabilitation procedures. Botulinum neurotoxin type A (BoNT-A) represents the gold standard therapy for tone modulation in focal spasticity and related disorders also in acquired brain injury including stroke. In general, treatment with BoNT-A is performed in addition to other rehabilitation strategies based on individualized multidisciplinary programs aimed at achieving tailored goals for each patient. The efficacy and safety of different BoNT-A formulations for spasticity have been demonstrated for labeled doses[5,6]. However, in multifocal disabling upper and/or lower limb spasticity, total doses required to fulfill goal achievement and patients' needs may exceed those currently approved. In recent years, higher doses have been used, especially in case of upper and lower limb severe spasticity considering the low prevalence of complications and the reversibility of the BoNT-A[7]. Patients with multifocal spasticity may benefit from BoNT-A treatment with higher total doses than currently recommended by the prescribing information of different formulations available. The prospective, single-arm, dose-titration TOWER study proved the safety and efficacy of incobotulinumtoxinA (IncoBoNT-A) in doses up to 800 U[8]. Ianieri et al[9], in a retrospective, observational study involving 120 patients with severe spasticity, also demonstrated long-term (2 years) efficacy of IncoBoNT-A for the treatment of muscle spasticity using variable doses (from 100 to 1000 U), according to individual needs. These studies introducing IncoBoNT-A high dose therapy (up to 1000 U) demonstrated that escalating IncoBoNT-A doses did not compromise safety or tolerability and was associated with increased treatment efficacy[6,7]. Recent consensus guidelines trying to optimize botulinum toxin therapy are in agreement with the concept of individualized dosing scheme therapy[10] .

The objective of the present retrospective study was to provide real-world evidence of the effectiveness and tolerability of IncoBoNT-A, at doses according to individual needs, in patients with ABI and severe upper and lower limb spasticity.

2. MATERIAL and METHODS

2.1. Study design

This retrospective observational monocentric cohort study evaluated data from patients with a confirmed diagnosis of ABI who experienced severe upper and/or lower limb spasticity at the Hospital La Magdalena (Castellón, Spain) between 2005 and 2017. Study data were retrospectively extracted from the patients´ medical history kept at the electronic medical system of the Hospital.

Criteria for inclusion in the study were: adult male and female (over 18 years); diagnosis of severe multifocal spasticity due to ABI and signing informed consent. Exclusion criteria included those related to the contraindication of the injection, i.e. coagulation disorders, infection or inflammation at the proposed injection site; hypersensitivity to the active substance or any of the excipients; or generalized disorders of muscle activity. Patients received a multipattern periodic treatment with ultrasound (US)-guided injections of incobotulinumtoxinA at doses according to their needs. Previous doses resulted in unsatisfactory outcomes, thus higher (individualized) doses were expected to achieve a satisfactory clinical improvement. In this study, a pretest-posttest and quasi-experimental design was used. This study was approved by the Ethics Committee of Hospital General Universitario of Castellón (Castellón, Spain).

2.2. Studied variables

Variables collected from patients included: demographic variables (gender, age), clinical variables (type of central nervous system – CNS – lesion, severity degree of the spasticity secondary to the CNS lesion, muscular tone, pain score, articular range of motion – ROM – assessment, quality of life of the patient, treatment satisfaction and treatment-related adverse effects), and variables related to the botulinum toxin injection (injected muscles and doses injected per muscle). Clinical assessments were performed at the injection visit (pre-injection) and 4 weeks after the injections. The pain was assessed using a visual analogue scale (VAS, 0-10). The muscular tone was determined by using the Ashworth scale, scoring from 0 (no increase in tone) to 4 (limb rigid in flexion or

extension). Goniometry was used for the assessment of passive ROM. Movements of the gleno-humeral joint were also evaluated. The satisfaction with the treatment was analyzed using a 5-point Likert scale, scoring from -2 (much worse) to +2 (much improved).

2.3. Statistical analysis

All eligible men and women with ABI were included in the analysis. Results were evaluated using descriptive analyses, and no a priori hypothesis for statistical testing was defined.
Continuous variables were expressed as mean, range (minimum-maximum values) and standard deviation (SD), whereas categorical ones as absolute and relative frequencies. Differences in VAS and Ashworth Scale between pre-injection and four weeks post-injection were analyzed with the p-paired t-test. Statistical significance was established with $p<0.05$. All statistical procedures were carried out with SAS 9.4 software.

3. RESULTS

3.1. Population

Adult men and women with cerebrovascular accident (CVA) and upper and/or lower limb multifocal severe spasticity were eligible for inclusion if they had received total body doses of at least 800 U IncoBoNT-A. These doses were deemed necessary by the physician for the treatment of their severe spasticity. Ten patients included in the study. They had a mean age of 62.3 years (range: 40-77; Table 1). Six of them suffered from an ischemic CVA, and 4 from a hemorrhagic CVA. The ischemic CVA occurred in the right (n= 5) or left (n=1) middle cerebral artery. Seven and three patients experienced right or left hemiplegia, respectively. At the pre-injection, the mean Barthel index was 78.5 (range: 50-95), the mean VAS was 4.7 (range: 3-7), and the mean Ashworth scale was 2.5 (range: 1-3).

Table 1. Characteristics of patients at pre-injection

	Patients (N = 10)
Age, mean years (range)	62.3 (40-77)
Diagnosis of CVA, n (%)	
Hemorrhagic	4 (40.0)
Ischemic	6 (60.0)
Hemiplegia	
Right	7 (70.0)
Left	3 (30.0)
Assessment scales, mean (range)	
Barthel Index (0-100)	78.5 (50-95)
VAS	4.7 (3-7)
Ashworth Scale	2.5 (1-3)

n (%), number of patients (percentage of patients); CVA, cerebrovascular accident; VAS, visual analogue scale

3.2. IncobotulinumtoxinA injections

Forty injections of 800 U and 2 of 900 U were administered in total to these 10 patients. The mean number of injection cycles per patient was 4.2 (range: 1-6; Table 2). A total of 77 muscles were injected (a mean of 7.7 muscles per patient). All patients were injected in the *flexor digitorum superficialis*, and 9 out of 10 patients in the *flexor digitorum profundus*, *triceps surae* and *biceps*. The mean duration of the treatment was 4.1 months (range: 3-6). The VAS score for pain decreased significantly from pre-injection (mean: 4.7; SD: 1.3) to four-week post-injection (mean: 0.7; SD: 1.1; p= 0.001; Table 3). Similarly, the mean Ashworth Scale score at four-week post-injection (mean: 1.4; SD: 0.6) was significantly lower than at injection (mean: 2.5; SD: 0.6; p= 0.001). Except for two patients in one pattern, all patients showed an improvement in passive ROM assessments (Table 4). All patients reported maximum satisfaction with the treatment, all reporting "much improved" after the treatment. No treatment-related adverse effects were observed during the study period.

Table 2. Information on incobotulinumtoxinA injections

	Patients (N = 10)
Mean number of injection cycles (range)	4.2 (1-6)
Number of injections, n (%)	
1	2 (20.0)
2	0 (0.0)
3	1 (10.0)
4	2 (20.0)
5	1 (10.0)
6	4 (40.0)
Injected muscles, m / n (%)	77 / 10 (100.0)
Flexor digitorum superficiales	10 / 10 (100.0)
Flexor digitorum profundus	9 / 9 (90.0)
Triceps surae	9 / 9 (90.0)
Biceps brachii	9 / 9 (90.0)
Pronador teres	7 / 7 (70.0)
Flexor carpi radialis	6 / 6 (60.0)
Soleus	5 / 5 (50.0)
Brachialis	5 / 5 (50.0)
Tibialis posterior	3 / 3 (30.0)
Triceps brachii	3 / 3 (30.0)
Extensor carpi radialis	3 / 3 (30.0)
Peroneus longus	2 / 2 (20.0)
Rectus femoris	1 / 1 (10.0)
Supinator	1 / 1 (10.0)
Hamstring	1 / 1 (10.0)
Interossei dorsalis pedis	1 / 1 (10.0)
Duration of treatment, mean months (range)	4.1 (3-6)

n (%), number of patients (percentage of patients); m, number of muscles

Table 3. Change in pain and muscular tone assessments between pre-injection and four weeks after the last injection

	Mean score (SD)	**Mean difference (95% CI)**	**p***
Pain assessment (VAS, 0-10)			
Pre-injection	4.7 (1.3)		
Four weeks after last injection	0.7 (1.1)	-4.0 (-5.2, -2.7)	0.001
Muscular tone assessment (Ashworth Scale, 0-4)			
Pre-injection	2.5 (0.6)		
Four weeks after last injection	1.4 (0.6)	-1.1 (-1.2, -0.9)	0.001

SD, standard deviation; 95% CI, 95% confidence interval; VAS, visual analogue scale
* paired t-Student

Table 4: Results on the passive range of motion using goniometry

PATIENT 1	**PRE-INJECTION**	**4 WEEKS POST-INJECTION**	**ROM GAIN**
Elbow	EXTENSION: -60° SUPINATION: -30°	EXTENSION: -40° SUPINATION: -0°	+20° +30°
Wrist	DORSIFLEXION: -30°	DORSIFLEXION; -10°	+40°
Hand MCP	EXTENSION: -65°	EXTENSION: 0°	+65°
Foot	IN 20° INVERSION NO REDUCTION	NEUTRAL	+20°
Ankle	DORSIFLEXION: -45°	DORSIFLEXION: -0°	+45°
PATIENT 2			
Elbow	EXTENSION: -10° SUPINATION: -50°	EXTENSION: 0° SUPINATION: -5°	+10° +45°
Wrist	DORSIFLEXION: -0°	DORSIFLEXION: 40°	+40°
Hand MCP	EXTENSION: -75°	EXTENSION: 0°	+75°
Ankle	DORSIFLEXION: -10°	DORSIFLEXION: -10°	+0°
PATIENT 3			
Shoulder	ANTEPULSION: 90° ABDUCTION: 45°	ANTEPULSION: 130° ABDUCTION: 110°	+40° +65°
Elbow	EXTENSION: -35° SUPINATION: -20°	EXTENSION: 0° SUPINATION: -5°	+35° +15°

Hand MCP	EXTENSION: -85°	EXTENSION: -10°	+75°
Ankle	DORSIFLEXION: -10°	DORSIFLEXION: -10°	+0°
PATIENT 4			
Shoulder	ANTEPULSION: 100° ABDUCTION: 120°	ANTEPULSION: 120° ABDUCTION : 140°	+20° +20°
Elbow	EXTENSION: -25° SUPINATION: -30°	EXTENSION: 0° SUPINATION: -5°	+25° +25°
Wrist	DORSIFLEXION: 20°	DORSIFLEXION: 30°	+10°
Knee	FLEXION: 90°	FLEXION: 130°	+40°
Ankle	DORSIFLEXION: -15°	DORSIFLEXION: 0°	+15°
PATIENT 5			
Elbow	EXTENSION: -30°	EXTENSION: 0°	+30°
WRIST	PALMAR FLEXION: -45°	PALMAR FLEXION: +15°	+60°
Hand MCP	EXTENSION: -75°	EXTENSION: 0°	+75°
Ankle	DORSIFLEXION: -10°	DORSIFLEXION: 0°	+10°
PATIENT 6			
Elbow	EXTENSION: -30° SUPINATION: -45°	EXTENSION: 0° SUPINATION: 0°	+30° +45°
Wrist	DORSIFLEXION: -10°	DORSIFLEXION: 0°	+10°
Hand MCP	EXTENSION: -45°	EXTENSION: 0°	+45°
PATIENT 7			
Elbow	EXTENSION: -60° SUPINATION: -35°	EXTENSION: 0° SUPINATION: -5°	+60° +30°
Wrist	DORSIFLEXION: -10°	DORSIFLEXION: +40°	+50°
Hand (MCP)	EXTENSION: -65°	EXTENSION: 0°	+65°
Ankle	DORSIFLEXION: -15°	DORSIFLEXION: 0°	+15°
Foot	EVERSION: -20°	EVERSION: 10°	+30°
PATIENT 8			
Shoulder	ABDUCTION: 100°	ABDUCTION : 130°	+30°
Elbow	FLEXION: 40° SUPINATION: -50°	FLEXION: 90° SUPINATION: -20°	+50° +30°
Wrist	DORSIFLEXION: -30°	DORSIFLEXION: 0°	+30°
Hand	EXTENSION: -75°	EXTENSION: 0°	+75°
Ankle	DORSIFLEXION: -10°	DORSIFLEXION: 0°	+10°
PATIENT 9			
Shoulder	ABDUCTION: 90°	ABDUCTION: 120°	+30°
Elbow	EXTENSION: -30°	FLEXION: 0°	+30°
Hand	EXTENSION: -75°	EXTENSION: 0°	+75°
Ankle	DORSIFLEXION: -10°	DORSIFLEXION: 0°	+10°
PATIENT 10			
Shoulder	ABDUCTION: 90°	ABDUCTION: 130°	+40°
Elbow	FLEXION: 90° EXTENSION: -40° PRONATION: -30°	FLEXION: 110° EXTENSION: -20° PRONATION: 0°	+20° +20° +30°
Hand	EXTENSION: -65°	EXTENSION: 0°	+65°
Knee	EXTENSION: -45°	EXTENSION: -30°	+15°
Ankle	DORSIFLEXION: -10°	DORSIFLEXION: 0°	+10°

ROM, range of motion; MCP, metacarpophalangeal joint

4. DISCUSSION

Patients with upper and lower limb severe spasticity are complex for treatment planning[3]. The aim of the treatment with botulinum toxin in these patients is not only to improve their functionality, in many cases, the goal is to improve joint ranges of motion and muscle extensibility to facilitate care, hygiene and even improve limb posture. Moreover, it has been suggested that incobotulinumtoxinA increased quality of life by improving movement, daily activities, mental health, and muscle tone more effectively than conventional therapy[11].

One of the problems usually found in patients with severe impairment is that the maximum recommended authorized dose is not enough for patients´ needs. This is the reason why, in recent years, there is a tendency to use higher doses, especially in case of upper and lower limb severe spasticity considering the low prevalence of complications and the reversibility of the BoNT-A[7]. Besides, the precision of the injection has improved a lot with the use of advanced instrumental guidance techniques like electrical stimulation or ultrasonography, allowing a correct muscle identification which may reduce the spread

of the toxins to the nearby tissues thus reducing the risk of adverse effects.

Among the botulinum toxin A formulations, IncoBoNT-A presents the particular feature that it is a 150 kDA purified neurotoxin, free from accessory complexing proteins. The advantage of the absence of complexing proteins could be related to a lower risk of immunogenicity as has been demonstrated recently in the first comparative study showing a statistically significant difference in antigenicity between the different licensed BoNT-A formulations[12].

The use of incobotulinumtoxinA is effective in the treatment of patients affected by spasticity[13-14]. In addition, Cordero-García and Sáenz de Tejada Sánchez indicated the benefits and safety of the use of incobotulinumtoxinA for early treatment of post-stroke spasticity in patients with SARS-COV-2[15]. Individualized doses of incobotulinumtoxinA allow increasing the doses per muscle within the recommended range and, therefore, treating more spasticity patterns and muscles according to the objectives and needs of the patients, as demonstrated in the TOWER study aimed at investigating the efficacy and safety in a dose titration study with IncoBoNT-A in upper and lower limb spasticity of cerebral causes in 155 subjects deemed to require total body doses of 800 U. The results of TOWER have been subsequently confirmed by Ianieri et al[9] and included in consensus guidelines[10] . In a recent work, Paba Dotes and De Torres-Gárcia showed that the use of incobotulinumtoxinA at high doses and short intervals (the first infiltration was 800 U, the second 800 U, and the last 500 U over 14 weeks) waseffective in a 16-year-old patient with a history of quadriplegia due to acquired brain damage secondary to thrombosis of the dural sinus. In this case, the individualized treatment schedule with incobotulinumtoxinA doses and dosing intervals designed to the patient and medical needs resulted in good clinical outcomes and good tolerability[16]. A phase 3 study, demonstrated that incobotulinumtoxinA used according to an individualized treatment plan within standardized guidelines is beneficial in improving muscle tone and motor function for children with spasticity-related cerebral palsy[17].

In our study, patients with multifocal spasticity have significantly benefited from IncoBoNT-A treatment with high individualized total doses as have been seen in the clinical parameters assessed at baseline and 4 weeks after treatment, such as pain control, muscle tone reduction and passive range of motion gained. It is important to emphasize that the doses per muscle were always within the recommended ranges and the number of muscles and spasticity patterns treated were always in accordance with the needs and goals of the patients. In addition to the reduction of muscle tone and improvement of limb functionality, pain relief may be considered an important treatment goal. Furthermore, pain relief may also maximise gains in other treatment domains, such as improved mobility, independence in daily activities, sleep, quality of life, etc. The results obtained on pain relief in this study are in agreement with those recently published from a pooled analysis on pain reduction in adults with limb spasticity following treatment with IncoBoNT-A[18].

After treating these severe spastic patients, no new safety issues arose with incobotulinumtoxinA doses of 800-900 U and up to 6 injection cycles. Each one of the patients, as well as their caregivers, were satisfied with the dose increase as the spasticity improved and it was well tolerated as none of them experienced side effects or atypical symptomatology. The results observed in this group of patients treated in a real clinic setting show that individualized doses of IncoBoNT-A, highly purified 150 kDa core neurotoxin protein, are effective and well-tolerated for this type of patient and as more clinical spasticity patterns can be treated allowing a greater focus on patient´s needs and goals and better management of their severe spasticity. Therefore, individualization of doses should be taken into account for optimizing clinical outcomes and improving the patient's treatment satisfaction.

Some authors agree that botulinum toxin therapy should be complemented by physiotherapy[19]. Others, advise the use of botulinum toxin therapy combined with any other anti-dystonic therapy including oral drugs, intrathecal baclofen and peripheral or central surgery including deep brain stimulation [20]. The strengths of this study include our patient focus approach to treatment, with individualized treatment options. Moreover, the study design allowed for the treatment of several muscle groups. Given the limited number of patients, the results reported here will provide a valuable starting point for future research in this field. However, our findings represent a positive and promising future regarding treatment and recovery for patients with brain injury and severe upper and lower limb spasticity.

5. CONCLUSION

Our results suggest that the repeated administration of doses, adapted to individual needs, allows the treatment of a higher number of spasticity patterns and the increase of treatment efficacy by an improvement of pain, muscular tone and articular balance, without the development of adverse effects.

Conflicts of Interest Statement: The authors have no conflicts of interest to declare.

Funding Statement: The data analysis and medical writing was supported by unrestricted funding by Merz Pharma España, S.L.

Author Contributions: M.H.A. and N.C.A. designed the study, collected and analyzed the data, and reviewed the manuscript. A medical writer from Meisys (Spain) wrote the manuscript. The authors have read and agreed to the published version of the manuscript.

REFERENCES

1. Saatman KE, Duhaime AC, Bullock R, Maas AI, Valadka A, Manley GT. Classification of traumatic brain injury for targeted therapies. J. Neurotrauma. 2008;25:719–738. doi: 10.1089/neu.2008.0586.

2. Ada L, O'Dwyer N, O'Neill E. Relation between spasticity, weakness and contracture of the elbow flexors and upper limb activity after stroke: an observational study. Disability and Rehabilitation. 2006;28(13-14):891-897. doi:10.1080/09638280500535165

3. Pandyan A, Gregoric M, Barnes M, Wood D, Wijck F, Burridge J, et al. Spasticity: clinical perceptions, neurological realities and meaningful measurement. Disability and Rehabilitation. 2005;27(1-2):2-6. doi:10.1080/09638280400014576

4. McGuire J. Epidemiology of spasticity in the adult and child. In: Brashear A editor(s). Spasticity: Diagnosis and Management. 2nd Edition. New York (NY): Demos Medical Publishing, 2016.

5.Elovic EP, Munin MC, Kanovsk ! ý P, Hanschmann A, Hiersemenzel R, Marciniak C. Randomized, placebo controlled trial of incobotulinumtoxinA for upper-limb post-stroke spasticity. Muscle Nerve 2016;53:415–421.

6.Kaji R, Osako Y, Suyama K, Maeda T, Uechi Y, Iwasaki M. Botulinum toxin type A in post-stroke lower limb spasticity: a multicenter, double-blind, placebo-controlled trial. J Neurol 2010;257:1330–1337.

7. Santamato A, Ranieri M, Solfrizzi V, Lozupone M, Vecchio M, Daniele A, Greco A, Seripa D, Logroscino G, Panza F. High doses of incobotulinumtoxinA for the treatment of post-stroke spasticity: are they safe and effective?. Expert Opin Drug Metab Toxicol. 2016; 12(8); 843-846.

8. Wissel J, Bensmail D, Ferreira JJ, Molteni F, Satkunam L, Moraleda S, et al. Safety and efficacy of incobotulinumtoxinA doses up to 800 U in limb spasticity: the TOWER study. Neurology. 2017;88(14):1321-1328. doi:10.1212/WNL.0000000000003789

9. Ianieri G, Marvulli R, Gallo GA, Fiore P, Megna M. "Appropriate treatment" and therapeutic window in spasticity treatment with incobotulinumtoxinA: From 100 to 1000 units. Toxins (Basel). 2018;10(4):140. doi:10.3390/toxins10040140

10. Dressler D, Altavista MC, Altenmueller E, Bhidayasiri R, Bohlega S, Chana P, et al. Consensus guidelines for botulinum toxin therapy: general algorithms and dosing tables for dystonia and spasticity. J Neural Transm (Vienna). 2021;128(3):321-335. doi:10.1007/s00702-021-02312-4

11. Turcu-Stiolica A, Subtirelu MS, Bumbea AM. Can Incobotulinumtoxin-A Treatment Improve Quality of Life Better Than Conventional Therapy in Spastic Muscle Post-Stroke Patients? Results from a Pilot Study from a Single Center. Brain Sci. 2021 ;11(7):934. doi: 10.3390/brainsci11070934.

12. Hefter H, Rosenthal D, Jansen A, Brauns R, Ürer B, Bigalke H, et al. Significantly lower antigenicity of incobotulinumtoxin than abo- or onabotulinumtoxin. J.Neurol 2022; doi: 10.1007/s00415-022-11395-2.

13. Simpson DM, Hallett M, Ashman EJ, Comella CL, Green MW, Gronseth GS, et al. Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2016;86(19):1818-26. doi: 10.1212/WNL.0000000000002560.

14. Ro T, Ota T, Saito T, Oikawa O. Spasticity and Range of Motion Over Time in Stroke Patients Who Received Multiple-Dose Botulinum Toxin Therapy. J Stroke Cerebrovasc Dis. 2020;29(1):104481. doi: 10.1016/j.jstrokecerebrovasdis.

15. Cordero-García C, Sández de Tejada Sánchez MM. Benefit and Safety of Incobotulinumtoxina for Early Management of Post-Stroke Spasticity In A Patient With Sars-Cov-2: A Case Report. JRM-CC. 2021; 4(1000065): doi: 10.2340/20030711-1000065

16. Paba Dotes AB and De Torres-Gárcia I. Management of Spasticity Caused by Thrombotic Brain Injury with Incobotulinumtoxina in a Young Patient: A New Paradigm, Medical Research Archives, [online] 2022; 10(6). https://doi.org/10.18103/m ra.v10i6.2836

17. Heinen F, Kanovský P, Schroeder AS, Chambers HG, Dabrowski E, Geister TL, Hanschmann A, et al. IncobotulinumtoxinA for the treatment of lower-limb spasticity in children and adolescents with cerebral palsy: A phase 3 study. J Pediatr Rehabil Med. 2021;14(2):183-197. doi: 10.3233/PRM-210040.

18. Wissel J, Camões-Barbosa A, Comes G, Althaus M, Scheschonka A and Simpson D. Pain Reduction in Adults with Limb Spasticity Following Treatment with IncobotulinumtoxinA: A Pooled Analysis. Toxins 2021, 13, 887. https://doi.org/10.3390/toxins13120887

19. Dressler D, Adib Saberi F. Rehabilitation of dystonia. In: Chien HF, Barsottini O (eds) Movement disorders rehabilitation. Springer, New York, 2017: 67–82

20. Dressler D, Adib Saberi F, Rosales RL. Botulinum toxin therapy of dystonia. J Neural

Transm (Vienna). 2021; 128(4):531-537. doi: 10.1007/s00702-020-02266-z.