Switching from OnabotulinumtoxinA to AbobotulinumtoxinA in Children with Cerebral Palsy Treated for Spasticity: A Retrospective Safety Evaluation

Nigar Dursun, Melike Akarsu, Tugba Gokbel, Merve Akyuz, Cagla Karacan, Erbil Dursun

Kocaeli University Faculty of Medicine Department of Physical Medicine and Rehabilitation

CXX

INTRODUCTION

- Hypertonia is the most common motor disorder seen in cerebral palsy (CP), and if inadequately managed, can result in slowly developing secondary problems including soft tissue contractures and bone deformities that further complicate effective long-term management.
- Clinical guidelines recommend the use of botulinum neurotoxin-A (BoNT-A) for localized/segmental spasticity[1-4] and repeated use of BoNT-A treatments in an integrated approach has enabled a prevention or delay in the development of contractures and bone deformities, thereby reducing the need for orthopedic surgery.[5]
- Several BoNT-A products are available, but there are no controlled head to head clinical trials comparing efficacy and safety of the different formulations in patients with CP and other neurological conditions.
- In clinical practice, there are often many factors that impact the choice of product, from the clinician's own experience and preferences to hospital formulary decisions. Usually, a patient will continue with the first injected product. However, circumstances such as administrative changes can restrict the choices available to the clinician.
- However, there is little information on the efficacy and safety of continued treatment when children are switched from one product to another.

OBJECTIVE

- We present here the results of a single centre retrospective study of children switching from onabotulinumtoxinA (OnaBoNT-A) to abobotulinumtoxinA (AboBoNT-A) due to changes in administrative processes and reimbursement policies.
- The main aims of analysis were to explore whether switching from OnaBoNT-A to AboBoNT-A is safe and well-tolerated and whether therapeutic efficacy is maintained from one product to another.

METHODS

- This was a retrospective, single centre, observational study conducted at the Kocaeli University Department of Physical Medicine and Rehabilitation, which is active in clinical research and routinely collects detailed clinical assessment data.
  - Routine assessments include the Modified Ashworth Scale (MAS), Tardieu Scale and Observational Gait Scale (OGS).
- All children with a diagnosis of CP (GMFCS levels I-V) and lower limb hypertonia treated between 2007 to 2017 were included in this retrospective analysis. Children had to have had at least 2 consecutive cycles of BoNT-A treatment, one cycle with OnaBoNT-A and one with AboBoNT-A.
- Injection parameters were individualized according to the goals of treatment, motor severity, accompanying disturbances, age and weight of the patient, body region, the size of the targeted muscle(s), neuro-muscular junction distribution for the muscle(s) and previous BoNT- A experience. There was no dose conversion ratio applied during the change of treatment, all children were individually evaluated.
- Information on AEs and their relation to BoNT-A treatment was collected for the final OnaBoNT-A treatment cycle prior to switch, and for the first AboBoNT-A treatment cycle following switch. Data were collected until the following treatment cycle or for a post-treatment period of 6 months after switch.
- We also assessed whether therapeutic efficacy was maintained with the product switch.

RESULTS

Baseline characteristics, associated conditions and type of adjunctive therapy.

Baseline Characteristics	N=118
Sex (Male/Female); n (%)	81 (68.6)/ 37 (31.4)
Age (months); Mean ± SD	81.4 ± 38.9
Type of hypertonia; n (%)	
Spastic	65 (55.1)
Mixed	53 (44.9)
Type of involvement; n (%)	
Unilateral	23 (19.5)
Bilateral	95 (80.5)
Gross Motor Function Classification System Level; n (%)	
Level I	9 (7.6)
Level II	35 (29.7)
Level III	19 (16.1)
Level IV	50 (42.4)
Level V	5 (4.2)
Associated Conditions; n (%)	
Intellectual disability	16 (13.6)
Epilepsy	30 (25.4)
Speech and communication difficulties	22 (18.6)
Swallowing problems	13 (11.0)
Behavioral disorders	18 (15.3)
Bladder and/or bowel incontinence	51 (43.2)
Strabismus and/or visual disorders	56 (47.5)
Adjunctive Therapies; n (%)	
Onabotulinumtoxin-A:	
Intensive therapy	83 (70.3)
Serial casting	41 (34.7)
Hippotherapy	17 (14.4)
Robotic rehabilitation	5 (4.2)
Abobotulinumtoxin-A:	
Intensive therapy	67 (56.8)
Serial casting	33 (28.0)
Hippotherapy	13 (11.0)
Robotic rehabilitation	12 (10.2)

Mean (SD) dosages per muscle (U/kg) in OnaBoNT-A and AboBoNT-A treatment cycles

Dose per muscle in most affected leg (n = OnaBoNT-A/AboBoNT-A)	OnaBoNT-A treatment cycle (n=118)	AboBoNT-A treatment cycle (n=118)
Iliopsoas (n=74/68)	0.7 ± 0.3	2.3 ± 0.9
Hip adductors (n=43/43)	1.2 ± 0.5	3.3 ± 1.3
Rectus femoris (n=61/73)	1.2 ± 0.8	3.0 ± 1.6
Gracilis (n=64/77)	0.8 ± 0.5	2.4 ± 1.1
Hamstrings (n=93/102)	1.7 ± 1.0	4.2 ± 2.2
Gastrocnemius (n=111/117)	2.5 ± 1.2	5.8 ± 2.9
Soleus (n=85/99)	1.2 ± 0.8	3.2 ± 1.6
Tibialis posterior (n=65/60)	1.2 ± 0.7	3.2 ± 1.8
Peroneal muscles (n=32/34)	0.6 ± 0.3	1.8 ± 0.9
Flexor digitorum longus (n=41/54)	0.6 ± 0.3	1.8 ± 0.7

TEAEs were recorded in 41 (34.7%) patients in the OnaBoNT-A treatment cycle versus 31 (26.3%) patients in the AboBoNT-A treatment cycle

	OnabotulinumtoxinA* (n=118)			AbobotulinumtoxinA** (n=118)		
	Frequency (Percent)	Treatment related	sAE	Frequency (Percent)	Treatment related	sAE
Upper respiratory tract infection	25(21.1)	No	No	19(16.1)	No	No
Raynauds phenomenon	1(0.8)	No	No	1(0.8)	No	No
Soft tissue surgery for lower extremity	1(0.8)	No	Yes	1(0.8)	No	Yes
Injection site pain	1(0.8)	Yes	No	3(2.5)	Yes	No
Injection site ecchymosis	3(2.5)	Yes	No	3(2.5)	Yes	No
Epileptic seizures	3(2.5)	No	No	-	-	-
Spinal surgery	2(1.6)	No	Yes	-	-	-
Hip surgery	2(1,6)	No	Yes	-	-	-
SDR	1(0.8)	No	Yes	-	-	-
Tonsillitis	1(0.8)	No	No	-	-	-
Oral ulceration	1(0.8)	No	No	-	-	-
Injection site nodule	1(0.8)	Yes	No	-	-	-
Eye surgery	1(0.8)	No	Yes	-	-	-
Herpes infection	-	-	-	1(0.8)	No	No
Spinal infection	-	-	-	1(0.8)	No	Yes
Knee effusion	-	-	-	1(0.8)	No	No
Falls	-	-	-	1(0.8)	Yes	No

* Overlap of AEs in 2 patients, **36 patients were not reinjected (continued follow-up)

Similar improvements in MAS and Tardieu Scale scores at Weeks 4-6 with OnaBoNT-A and AboBoNT-A treatment

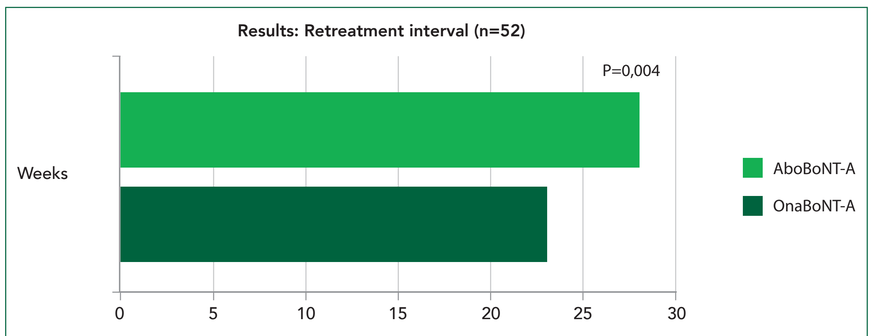
	Baseline			Mean Change		
	OnaBoNT-A (Mean ± SD)	AboBoNT-A (Mean ± SD)	p	OnaBoNT-A (Mean ± SD)	AboBoNT-A (Mean ± SD)	p
Hip adductors (Flexed knee)						
MAS	3.0 ± 1.0	2.9 ± 0.9	0.712	1.7 ± 0.6	1.9 ± 0.7	0.070
Tardieu scale						
Angle of arrest, XV1	41.0 ± 12.9	41.5 ± 14.3	0.907	9.4 ± 9.5	9.9 ± 10.6	0.717
Angle of catch, XV3	22.5 ± 9.6	23.4 ± 10.3	0.663	15.6 ± 12.5	16.6 ± 12.7	0.194
Spasticity grade, X	18.4 ± 10.3	17.9 ± 9.3	0.810	8.9 ± 10.5	9.9 ± 10.6	0.326
Spasticity angle, Y	2.0 ± 0.0	2.0 ± 0.0	-	0.5 ± 0.9	0.7 ± 0.9	0.083
Hip adductors (Extended knee)						
MAS	2.9 ± 1.0	2.7 ± 0.9	0.071	1.3 ± 0.6	1.4 ± 0.7	0.642
Tardieu scale						
Angle of arrest, XV1	30.8 ± 12.8	35,7 ± 15,2	0.544	9.8 ± 8.9	7.7 ± 9.6	0.657
Angle of catch, XV3	15.6 ± 8.3	20,4 ± 11,8	0.127	12.7 ± 12.5	14.0 ± 12.7	0.598
Spasticity grade, X	14.8 ± 8.1	15,8 ± 7,8	0.443	7.6 ± 9.2	10.2 ± 8.8	0.479
Spasticity angle, Y	2.0 ± 0.0	2.0 ± 0.0	-	0.3 ± 0.7	0.6 ± 0.9	0.183
Hamstrings						
MAS	2.9 ± 0.9	3.0 ± 0.8	0.306	1.5 ± 0.7	1.6 ± 0.7	0.167
Tardieu scale						
Angle of arrest, XV1	135.4 ± 17.7	133.9 ± 19.7	0.000	20.1 ± 22.8	18.5 ± 10.6	0.467
Angle of catch, XV3	105.3 ± 21.7	105.5 ± 23.0	0.172	27.5 ± 15.1	27.3 ± 14.3	0.873
Spasticity grade, X	30.0 ± 12.3	28.0 ± 14.2	0.040	15.9 ± 23.6	13.4 ± 10.5	0.291
Spasticity angle, Y	2.0 ± 0.1	2.0 ± 0.1	0.320	0.2 ± 0.7	0.3 ± 0.7	0.242
Plantar flexors (Flexed knee)						
MAS	3.1 ± 0.7	3.1 ± 0.7	0.765	1.8 ± 0.7	1.9 ± 0.7	0.348
Tardieu scale						
Angle of arrest, XV1	95.8 ± 11.2	96.2 ± 11.2	0.563	9.3 ± 6.9	10.3 ± 6.8	0.149
Angle of catch, XV3	74.0 ± 14.2	74.0 ± 14.0	0.830	18.8 ± 9.6	19.1 ± 10.1	0.796
Spasticity grade, X	22.3 ± 9.1	23.0 ± 15.6	0.700	10.7 ± 7.9	9.4 ± 7.8	0.071
Spasticity angle, Y	2.1 ± 0.3	2.1 ± 0.4	0.408	0.3 ± 0.6	0.3 ± 0.7	0.251
Plantar flexors (Extended knee)						
MAS	3.4 ± 0.6	3.4 ± 0,7	0.566	1.7 ± 0.6	1.7 ± 0.8	0.278
Tardieu scale						
Angle of arrest, XV1	85.4 ± 11.1	85.4 ± 11,7	0.875	10.2 ± 6.8	10.6 ± 6.8	0.560
Angle of catch, XV3	62.6 ± 14.3	62.9 ± 14	0.684	20.0 ± 10.7	20.5 ± 10.1	0.623
Spasticity grade, X	22.6 ± 9.3	22.5 ± 8.0	0.664	10.9 ± 8.1	10.3 ± 7.4	0.493
Spasticity angle, Y	2.1 ± 0.3	2.1 ± 0.4	0.368	0.1 ± 0.4	0.2 ± 0.6	0.070

For statistical analysis, Modified Ashworth Scale (MAS) scores are derived as: 0=0, 1=1, +1=2, 2=3, 3=4 and 4=5.

Similar improvements in OGS scores at Weeks 4-6 with OnaBoNT-A and AboBoNT-A treatment

OGS (n=105)	OnaBoNT-A treatment cycle	AboBoNT-A treatment cycle	p
Knee position in midstance	0.5 ± 0.7	0.4 ± 0.8	0.635
Initial foot contact	1.0 ± 0.7	0.9 ± 0.7	0.096
Foot contact at midstance	0.7 ± 1.3	0.6 ± 0.7	0.173
Timing of heel rise	1.1 ± 1.0	1.1 ± 0.8	0.812
Hindfoot at midstance	0.3 ± 0.7	0.3 ± 0.7	0.892
Base of support	0.5 ± 0.8	0.4 ± 0.7	0.463
Gait assistive devices	0.2 ± 0.5	0.1 ± 0.5	0.558
Total score	4.1 ± 2.2	3.8 ± 2.1	0.202

Of the 52 patients with evaluable data, the time to retreatment was longer with AboBoNT-A than with OnaBoNT-A



66 patients were excluded not yet received a BoNT-A injection following switch, and/or had delays to their treatment visit due to non-efficacy related reasons (OnaBoNT-A & AboBoNT-A: AEs 13.6% & 3.4%; social and personal reasons 23.7% & 4.2%; others 5.1% & 0.8%)

DISCUSSION

- The results of this study demonstrate that in children with CP, switching BoNT-A formulations from OnaBoNT-A to AboBoNT-A was safe and well-tolerated, and efficacy was maintained.
- Across both treatment cycles, treatment-related AEs were mostly localized and minor injection site reactions with no significant difference between OnaBoNT-A and AboBoNT-A treatment.
- To date, most published studies have focused on the gastrocnemius-soleus complex and/or hamstrings,[1,6] and our data provide a useful insight into practical dosing for other proximal muscles of the lower limb.
- In a subgroup analysis AboBoNT-A appeared to have a longer retreatment interval than OnaBoNT-A

PRESENTED AT
TOXINS 2019: Basic Science and Clinical Aspects of Botulinum and Other Neurotoxins, 16-19 January, 2019, Copenhagen, Denmark.

References

1. Delgado MR, Hirtz D, Aisen M, et al. Practice parameter: pharmacologic treatment of spasticity in children and adolescents with cerebral palsy (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 2010;74:336-43.
2. NICE. Guideline CG145. Spasticity in children and young people with non-progressive brain disorders: Management of spasticity and co-existing motor disorders and their early musculoskeletal complications. 2012.
3. Heinen F, Desloovere K, Schroeder AS, et al. The updated European Consensus 2009 on the use of Botulinum toxin for children with cerebral palsy. *Eur J Paediatr Neurol* 2010;14:45-66.
4. Strobl W, Theologis T, Brunner R, et al. Best clinical practice in botulinum toxin treatment for children with cerebral palsy. *Toxins* 2015;7:1629-48.
5. Molenaers G, Desloovere K, Fabry G, et al. The effects of quantitative gait assessment and botulinum toxin A on musculoskeletal surgery in children with cerebral palsy. J Bone Joint Surg Am 2006;88:161–70.
6. Delgado MR, Bonikowski M, Carranza J, et al. Safety and efficacy of repeat open-label AbobotulinumtoxinA treatment. J Child Neurol 2017; 32(13):1058-64.