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SHORT COMMUNICATION

SWITCHING FROM ONABOTULINUMTOXIN-A TO ABOBOTULINUMTOXIN-A IN CHILDREN WITH CEREBRAL PALSY TREATED FOR SPASTICITY: A RETROSPECTIVE SAFETY AND EFFICACY EVALUATION*

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Objectives: **To determine whether switching from onabotulinumtoxin-A to abobotulinumtoxin-A in children with cerebral palsy is safe and whether therapeutic efficacy is maintained.**

Methods: **This retrospective observational study of routine care included 118 children with cerebral palsy (mean age 81.4 months (standard deviation 38.9)) who had switched from onabotulinumtoxin-A to abobotulinumtoxin-A injections into their lower extremities due to a change in hospital policy. Analysis was limited to the final onabotulinumtoxin-A treatment-cycle prior to switch, and the first abobotulinumtoxin-A treatment-cycle following switch. The primary objective was to document the safety and tolerability of switching products. Efficacy endpoints included muscle tone, spasticity, and gait function based on Modified Ashworth Scale (MAS), Tardieu Scale (TS) and Observational Gait Scale (OGS) scores.**

Results: **Treatment-emergent adverse events were recorded in 41 (34.7%) and 31 (26.3%) patients during the onabotulinumtoxin-A and abobotulinumtoxin-A treatment cycles, respectively. Treatment-related adverse events were reported in 5 patients in the onabotulinumtoxin-A treatment-cycle vs 7 in the abobotulinumtoxin-A treatment-cycle ($p = 0.774$). Treatment efficacy (4–6 weeks post-treatment) was similar in the onabotulinumtoxin-A and abobotulinumtoxin-A treatment-cycles for all variables (MAS, TS, OGS).**

Conclusion: **In children with cerebral palsy, switching from onabotulinumtoxin-A to abobotulinumtoxin-A is safe and generally well-tolerated and therapeutic efficacy is maintained.**

Key words: botulinum toxin; cerebral palsy; spasticity; abobotulinumtoxin-A; onabotulinumtoxin-A; Dysport; Botox.

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LAY ABSTRACT

In the absence of head-to-head clinical trials, a retrospective observational study of 118 children with cerebral palsy who had switched botulinum toxin formulation (from onabotulinumtoxin-A to abobotulinumtoxin-A) due to a change in hospital policy was performed. The safety and tolerability profile of both formulations were similar. Likewise, the efficacy of treatment (measured 4–6 weeks post-injection) was found to be similar for all clinical measures assessed. This study indicates that switching from onabotulinumtoxin-A to abobotulinumtoxin-A is generally well-tolerated and therapeutic efficacy is maintained.

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. Lower limb problems in CP range from difficulties with gait, balance and endurance, to problems with hygiene, care and pain. As the child grows and develops, difficulties can evolve, with significant impact on the quality of life of the child and their family.

Clinical guidelines recommend the use of botulinum neurotoxin-A (BoNT-A) for localized/segmental spasticity that causes pain, compromises care and hygiene, impedes motor function, impedes tolerance to other treatment modalities, such as orthoses, and/or causes cosmetic problems in this population (1–4). Moreover, the use of repeat 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 orthopaedic surgery and lessening the complexity of surgery when still required (5). Several BoNT-A products are available, but there are no controlled head to head clinical trials comparing the 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

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with the first injected product. However, circumstances such as administrative changes can restrict the choices available to the clinician.

There is little information on the efficacy and safety of continued treatment when children are switched from one product to another. We report here the results of a single-centre retrospective study of children who switched from onabotulinumtoxin-A (OnaBoNT-A) to abobotulinumtoxin-A (AboBoNT-A) due to changes in administrative processes and reimbursement policies. The main aims of this 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 (KOU) Department of Physical Medicine and Rehabilitation (PMR), which is active in clinical research and routinely collects detailed clinical assessment data. The study was approved by the ethics committee of KOU School of Medicine and Research-Education Hospital (project number KU GOAEK 2017/90).

Patients and treatment setting

The only inclusion criteria for this retrospective analysis were a diagnosis of CP and lower limb hypertonia treated in KOU Department of PMR from 2007 to 2017. Children had to have had at least 2 consecutive cycles of BoNT-A treatment; one cycle with OnaBoNT-A and one with AboBoNT-A. Since the units of the toxins are specific to their preparation and not interchangeable, no conversion ratio or fixed dose was used; all patients were individually evaluated.

All BoNT-A injections were routinely administered under guidance (electrical stimulation with or without ultrasound); the use of sedation/anaesthesia depended on the individual patient. 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 experience with BoNT-A. Goals of treatment varied widely in line with the heterogeneity of the clinic population, and varied from improvement in running (e.g. to play football in children with Gross Motor Function Classification System (GMFCS) level I) to ease of nappy change.

All children were managed by a multidisciplinary team consisting of PMR physicians, physical therapists, occupational therapists and students, special education specialists, recreational sports specialists, and orthotists. Following each BoNT- A injection, the children entered a 3-week intensive rehabilitation programme (half day or full day), which can be extended for a further 3 weeks if robotic rehabilitation is employed. The programme typically started 7–10 days after BoNT-A injection, and was designed by the senior PMR physician according to individualized therapeutic goals. Available adjunctive treatments included serial casting, orthotics, physical therapy, occupational therapy, cognitive rehabilitation, special educational programmes, non-invasive brain stimulation with transcranial direct current, neurofeedback, biofeedback, whole-body vibration, Biodex balance training, electrical stimulation and other physical therapy modalities, activity-based models, including functional ambulation training, constraint-induced therapy, bilateral intensive therapy, hippotherapy, music therapy by singing or playing percussive instruments or moving and dancing to music, virtual reality and robotic rehabilitation.

Assessments

As per routine practice, comprehensive clinical assessments were performed at the start of each treatment cycle (baseline) with a follow-up at week 4–6 post-injection. Routine assessments include the Modified Ashworth Scale (MAS) and Tardieu Scale (TS). Although not all goals were related to gait, we routinely assess gait function using the Observational Gait Scale (OGS) for children with GMFCS levels I–IV. At each visit parents and caregivers are questioned regarding the occurrence of adverse events (AEs) and their temporal relationship to the BoNT-A injection.

The primary objective of the analysis was to document the safety of switching from OnaBoNT-A to AboBoNT-A. Information on AEs and their relation to BoNT-A treatment was collected for the final OnaBoNT-A treatment cycle prior to the switch, and for the first AboBoNT-A treatment cycle following the switch. Data were collected until the following treatment cycle or for a post-treatment period of 6 months after the switch. It was also assessed whether therapeutic efficacy was maintained with the product switch, where therapeutic effects on muscle tone and spasticity were evaluated using the MAS and TS, respectively, and gait function was assessed using the OGS.

Analysis

All statistical analyses were limited to the final OnaBoNT-A treatment cycle prior to the switch, and the first AboBoNT-A treatment cycle following the switch. The distribution of treatment emergent adverse events (TEAEs) and treatment-related AEs across the OnaBoNT-A and AboBoNT-A treatment cycles were compared using McNemar's test. Efficacy outcomes at 4–6 weeks post-injection were compared with the baseline of each treatment cycle. The mean change from baseline to week 4–6 in derived MAS score; mean change in angle of arrest at slow speed (XV1), angle of catch at fast speed (XV3), spasticity angle (X), and spasticity grade (Y) of TS from baseline to post-treatment week 4–6 for ankle plantar flexor, hamstring, hip adductor muscle groups; and mean change in OGS score for OnaBoNT-A and AboBoNT-A treatment cycles were compared using Students' *t*-test for paired data.

RESULTS

Retrospective analysis of case records identified 118 children with CP who fulfilled the inclusion criteria for this study. Baseline characteristics and type of adjunctive therapy given are provided in Table I. Over half (53.4%) were independent walkers and, of these, 30% used walking aids. Children had received a mean of 3.7 (SD 3.2) treatment cycles with OnaBoNT-A before switching to AboBoNT-A. Mean total doses were 227.4 U (standard deviation (SD) 63.1) (13.7 U/kg (SD 5.0)) for OnaBoNT-A and 708 U (SD 194.1) (36.3 U/kg (SD 13.3)) for AboBoNT-A. Table II

Table I. 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* (%)	
I	9 (7.6)
II	35 (29.7)
III	19 (16.1)
IV	50 (42.4)
V	5 (4.2)
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)

SD: standard deviation.

shows the mean doses per lower limb muscle in the 2 treatment cycles.

TEAEs were recorded in 41 (34.7%) patients in the OnaBoNT-A treatment cycle vs 31 (26.3%) patients in the AboBoNT-A treatment cycle (Table III). There were no significant differences in the distribution of TEAEs between the OnaBoNT-A and AboBoNT-A treatment cycles ($p=0.286$). Treatment-related AEs were reported for 5 (4.1%) patients in the OnaBoNT-A treatment cycle and 7 (5.8%) patients in the AboBoNT-A treatment cycle; all were mild and resolved in less than 4 weeks. There was no significant difference in the distribution of treatment-related AEs between the treatment cycles ($p=0.774$).

Table II. Mean dosages per muscle (U/kg) in onabotulinumtoxin-A (OnaBoNT-A) and abobotulinumtoxin-A (AboBoNT-A) treatment cycles

Dose per muscle in most affected leg ($n=$ OnaBoNT-A/ AboBoNT-A)	OnaBoNT-A treatment cycle ($n=118$) Mean (SD)	AboBoNT-A treatment cycle ($n=118$) Mean (SD)
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)

SD: standard deviation.

Baseline clinical measurements (MAS, TS and OGS) were generally well balanced between the 2 treatment cycles. MAS and TS scores at the hip adductors (flexed and extended knee), hamstrings and plantar flexors (flexed and extended knee) similarly improved with OnaBoNT-A and AboBoNT-A treatment with no statistically significant differences observed (Table IV). Mean change from baseline in OGS total score to week 4–6 was also similar (4.1 (SD 2.2) with OnaBoNT-A vs 3.8 (SD 2.1) with AboBoNT-A, $p=0.202$). Change in individual OGS items are shown in Table SI.

DISCUSSION

This retrospective study demonstrates that, in children with CP, switching BoNT-A formulations from

[1]http://www.medicaljournals.se/jrm/content/?doi=10.2340/16501977-2550

Table III. Adverse events in onabotulinumtoxin-A (OnaBoNT-A) vs abobotulinumtoxin-A (AboBoNT-A) treatment cycles

	Onabotulinumtoxin-A[a] ($n=118$)			Abobotulinumtoxin-A[b] ($n=118$)		
	Frequency (%)	Treatment-related	sAE	Frequency (%)	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

[a]Overlap of adverse events (AEs) in 2 patients; [b]36 patients were not reinjected (continued follow-up).
SDR: selective dorsal rhizotomy; sAE: severe adverse events.

Table IV. Improvement from baseline for Modified Ashworth Scale (MAS) and Tardieu Scale (TS) at 4–6 weeks post-injection

	Baseline			Mean change		
	OnaBoNT-A Mean (SD)	AboBoNT-A Mean (SD)	*p*-value	OnaBoNT-A Mean (SD)	AboBoNT-A Mean (SD)	*p*-value
Hip adductors (patient in supine position with 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 (patient in supine position with 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 (patient in supine position)						
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 (patient in supine position with 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 (patient in supine position with 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.
SD: standard deviation.

OnaBoNT-A to AboBoNT-A is safe and well-tolerated, and efficacy is maintained. The safety profiles of both OnaBoNT-A and AboBoNT-A were similar and consistent with the previous literature (6–8).

Of note, almost half (46.6%) of the patients in this analysis were GMFCS IV or V. Although there is little direct evidence in the literature, these patients are generally considered to be at a higher risk for AEs (9, 10). In their pragmatic retrospective study of 454 children treated with BoNT-A, Papavasilou et al. showed that adverse reactions were associated with GMFCS level and presence of epilepsy, but were mostly mild even for severely affected patients (11). Likewise, despite the relatively high proportion of more severely affected children in our data-set, treatment-related AEs were uncommon before and after the switch. 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. Overall, the most common TEAEs were common childhood infections, such as upper respiratory tract infection. Three patients with prior history of epilepsy experienced seizures during the OnaBoNT-A treatment cycle. Serious AEs occurred in 7 patients, and included various surgical operations in the OnaBoNT-A treatment cycle, and spinal infection and soft tissue surgery in the AboBoNT-A treatment cycle. There was no treatment-related serious AE in either treatment cycle.

At the doses used in this study, OnaBoNT-A and AboBoNT-A were similarly effective in reducing hypertonia and improving gait. On average, MAS scores typically improved by at least one grade from baseline across the different muscles injected, in both treatment cycles. Similar improvements in TS scores were also observed for both products. There was no loss of therapeutic benefit following the switch from long-term use of one product (children had received a mean of 3.7 OnaBoNT-A treatment cycles) to the other. This is in line with the recent Swedish study of children with CP that also followed their switch from OnaBoNT-A to AboBoNT-A (12). As in that study, we were obliged to switch products due to

changes in administrative processes and reimbursement policies. Unlike that study, however, we did not use a fixed conversion ratio of OnaBoNT-A to AboBoNT-A, instead preferring to base our dosing decisions on the child's individual presentation at that time. In recent years, there has been considerable disagreement between the various studies conducted on this issue and many authors have concluded that there can be no fixed dose ratio between the products (13, 14). To date, most published studies have focused on the gastrocnemius-soleus complex and/or hamstrings (1, 7), and our data provide a useful insight into practical dosing for other proximal muscles of the lower limb.

Limitations of the current study include the retrospective design (i.e. no blinding) and lack of standardization (all children were treated as per standard clinical practice, which is impacted by a variety of social, personal and economic factors). Our analyses were limited to the last cycle of OnaBoNT-A and first cycle of AboBoNT-A. More studies are needed to prospectively compare the various BoNT-A products over longer durations of repeated treatment cycles. Some of the patients treated with AboBoNT-A could not be included in our analyses of treatment intervals because they had not yet been reinjected at the time of cut-off. The main driver of the switch was a change in healthcare policy and not related to the individual therapeutic standpoint. It did not include any children with primary or secondary non-response to OnaBoNT-A.

In summary, in this preliminary report of our first experience of switching from OnaBoNT-A to AboBoNT-A, therapeutic efficacy was sustained and no safety concerns were identified. Most clinicians prefer to maintain their patients on the same treatment provided it is working, and switch only in cases of non-response. Our experience of a mandated switch for administrative reasons was positive, and should be reassuring to clinicians involved in the long-term management of children living with CP.

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