Long-term efficacy and tolerability of 4-monthly versus yearly botulinum toxin type A treatment for lower-limb spasticity in children with cerebral palsy

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LIST OF ABBREVIATIONS

BoNT-A	Botulinum toxin type A
MPAD	Maximum passive ankle dorsiflexion
LOCF	Last observation carried forward

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In this study, we compared the long-term efficacy and tolerability of two dosage regimens of the potent botulinum toxin type A (BoNT-A; Dysport; Ipsen Ltd, Slough, UK) in children with cerebral palsy (CP) and lower-limb spasticity. Children aged 1 to 8 years with diplegic CP who were able to walk (aided or unaided) were randomized (1:1) to 30 LD_{50} units/kg total body weight of BoNT-A (injected into gastrocnemius muscles) every 4 months or once yearly for 2 years in this multicentre, assessor-blinded, parallel-group study. In the 4-monthly group (n=110, 39 males, 71 females), mean age was 3 years 8 months (SD 1y 6mo, range 1–8y). In the yearly group (n=104, 47 males, 57 females), mean age was 4 years 4 months (SD 1y 6mo, range 2–8y). Both treatment groups had similar baseline Gross Motor Function Measure scores. At month 28 (primary endpoint; intention-to-treat group), median maximum passive ankle dorsiflexion was 12.00° in the 4-monthly and 11.00° in the yearly group. Between-group difference of 1.67° was not statistically significant (p=0.055). Other efficacy endpoints showed no significant difference between the regimens. The results of the study do not allow a clear conclusion of the preferred injection regimen.

Cerebral palsy (CP) is the most common cause of severe physical disability in childhood, affecting about 1 in 400 children.[1] Spastic CP involves hypertonic muscles and is the most common form of CP, occurring in approximately 60 to 70% of cases.[2,3] Although children with CP initially show no deformity, evidence shows that unrelieved spasticity leads to contracture and bony torsion,[4] and that the majority of children with lower-limb spasticity have problems walking.[5] Calf muscle spasticity is a major factor that can interfere with normal walking by preventing heel strike.[5]

Botulinum toxin type A (BoNT-A) offers a targeted form of therapy to reduce spasticity in specific muscle groups and has become a standard treatment alternative to systemic therapies such as baclofen.[6] Intramuscular injections cause localized chemodenervation and muscle relaxation by preventing the release of acetylcholine into the presynaptic cleft of the neuromuscular junction.[7] Chemodenervation and the subsequent muscle relaxation permit increased longitudinal growth of bones and joints for the duration of the toxin's paretic effect and may postpone or reduce the need for orthopaedic surgery.[8]

The benefit of BoNT-A therapy for lower-limb spasticity in children with CP has been established in randomized, placebo-controlled trials and open-label studies.[9–12] It is common practice in Europe to carry out BoNT-A

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injections every 16 weeks or as required to maintain response. In the authors' experience, however, many practitioners may repeat dosing less frequently than once every 4 months. Accordingly, we conducted this study to compare the long-term efficacy and tolerability of two dosage regimens of this potent BoNT-A formulation (repeat treatments once every 4 months vs once yearly) in children with CP and lower limb spasticity.

METHOD

This was a 2-year, multinational, multicentre, assessor-blinded, randomized, parallel-group study. Parents or guardians of children gave written informed consent before the study. The study was approved by the local ethics committee or institutional review board and conducted according to the principles of good clinical practice and the Declaration of Helsinki.

Participants

Children aged 1 to 8 years with a clinical diagnosis of diplegic CP were recruited by 18 European centres: Czech Republic (*n*=3), France (*n*=1), Italy (*n*=1), Poland (*n*=6), the Slovak Republic (*n*=2), Spain (*n*=4), and the UK (*n*=1). Participants had to be able to walk with or without a walking aid or orthosis, have the potential to benefit from injections of BoNT-A to the gastrocnemius (judged by the investigator), and be able to achieve 10° passive ankle dorsiflexion. Children were excluded from the study if the investigator perceived a clinical need for surgery to the affected limbs within 2 years, if they were judged to need multilevel injections of BoNT-A, or if they had a significant foot deformity, defined by the inability to obtain calcaneum neutral position during measurement of maximum passive ankle dorsiflexion (MPAD), for which the muscle was stretched passively to give maximum dorsiflexion with the knee in full extension. Also excluded were those who had received BoNT-A treatment during the 9 months before the study, with the exception of participants who had completed one of two previous trials of the study drug,[10,13] who could enter provided any treatment benefit had disappeared completely and any adverse events considered possibly or probably related to study medication had resolved. Other exclusion criteria were previous surgery on the affected muscle, previous treatment with phenol for lower-limb spasticity, known sensitivity to BoNT-A, generalized disorder of muscle activity (e.g. myasthenia gravis), use of aminoglycoside antibiotics or spectinomycin, treatment with an investigational drug within the 30 days before or during the study, and unwillingness or inability to comply with the protocol.

Interventions

Participants were randomized (1:1) to receive an injection of 30 LD_{50} units/kg total body weight of BoNT-A (Dysport, Ipsen Ltd, Slough, UK) once every 4 months (4-monthly group) or once yearly (yearly group). For all children weighing more than 33kg, the maximum total dose per treatment cycle was 1000 units. Note that the dose of BoNT-A, expressed as LD_{50} units, is not comparable among different formulations because of differing assay methods. The dose units given here are specific to Dysport. Over the 2-year study, participants in the yearly group were scheduled to three injection sessions (at baseline, year 1, and year 2); those in the 4-monthly group had seven sessions (at baseline and then 4-monthly up to 2 years). Participants (except those who withdrew from the study) were followed up 4 months after their last BoNT-A injection.

BoNT-A was divided equally between both limbs. The gastrocnemius muscle was injected in two locations: the junction of the proximal quarter and the distal three-quarters of the gastrocnemius, determined by palpating the femoral and calcaneal insertions. This injection technique, which was chosen to reflect clinical practice at the time of the study, was devised to standardize the study treatment. The injection volume at each site was 0.5mL (total injection volume 2.0mL); injections were given in conjunction with a sedative (e.g. midazolam) and a topical anaesthetic cream.

To compensate for the absence of a placebo control, which would not have been ethical in this population, an assessor-blind design was employed. An unblinded physician administered the injections of BoNT-A and maintained security for the randomization codes but during the study neither the blinded physician, who was responsible for assessing participants before and throughout the study, nor the study physiotherapist were aware of the treatment allocation. Patients and their parents or guardians were asked not to discuss their treatment with the blinded assessors.

Endpoints

The primary efficacy endpoint was maximum passive ankle dorsiflexion at month 28. Secondary efficacy measures were MPAD at months 4, 8, 12, 16, 20, and 24, change in MPAD over time, time to development of fixed contractures (defined as MPAD no better than –10° for either leg), a requirement for corrective surgery, time to referral for surgery to correct fixed contractures (at the discretion of the blinded physician), and Gross Motor Function Measure (GMFM) overall and goal total scores (at months 1, 4, 8, 12, 13, 16, 20, 24, 25, and 28).

The tertiary efficacy measures were subjective functional assessment of change in gait pattern (judged by the blinded

assessor and the parent or guardian at months 1, 13, and 25), global assessment of efficacy (judged by the blinded assessor and the parent or guardian at month 28 or withdrawal), and neutralizing-antibody status at baseline and study end.

Assessments

The same treatment-blinded pairs of assessors (physiotherapist and physician) took MPAD measurements at each study visit using a plastic manual goniometer (Phoenix Healthcare Products, Nottingham, UK) to a precision of 1°. To maximize the reliability and accuracy of the methodology, all assessors were trained to use the goniometer according to a standardized study protocol. The mean of three MPAD recordings on each leg at each visit was used in the analyses. The GMFM assessment was conducted by a GMFM-accredited study physiotherapist with the child barefoot. Subjective functional assessment of change in gait was measured using a simple 4-point scale (worse than baseline, no response, minimal response, or good response) designed to give an overall impression of treatment effect. Assessments were made by an individual who was familiar with each child's gait. The global assessment of efficacy was a simple, subjective, five-point assessment (greatly improved, improved, no change, worse, or much worse) of improvement from baseline (screening visit) in gait pattern and quality of life. Neutralizing antibodies to BoNT-A were determined at a central laboratory (Wickham Laboratories Ltd, Hampshire, UK) using the mouse LD_{50} bioassay.

Patients were considered to have completed the study if they had attended the month 28 assessment or if surgical intervention was required before this time. Patients who were referred for such surgery completed month 28 assessments at the time of referral.

All adverse events were coded using the Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) 1995 dictionary. All serious adverse events and those associated with withdrawal were summarized, as were adverse events by treatment group, intensity, and relationship to study drug.

Statistical analysis

A mean between-group difference in MPAD of 5° was considered clinically significant and, assuming a standard deviation of 10°,[14] a total of 86 participants per group was required to detect a difference of 5° with 90% power and a 0.05 significance level. The study was powered to allow for a dropout rate of approximately 25%. All efficacy analyses were performed on the intention-to-treat population, which was the same as the safety population, and all statistical tests were two-sided. A per-protocol analysis was also performed for the primary endpoint.

Summary statistics were presented for MPAD, GMFM scores and neutralizing antibody status. Analysis of covariance (ANCOVA) was used to assess MPAD at month 28 and a model consisting of treatment, centre, and MPAD for the corresponding leg recorded at baseline was fitted to the data. If the assumptions of normality of residuals and homogeneity of variance were not satisfied, a non-parametric analysis using the Wilcoxon rank sum test or an appropriate transformation of the data was performed. For time to development of fixed contractures and time to referral for surgery to correct fixed contractures, Kaplan–Meier estimates of the distribution of time to these events at each time point were calculated for each group. The Cox proportional hazards regression model was used to test for differences between the groups in time to development of and time to referral for fixed contractures. A model consisting of treatment and centre (as an indicator variable) was fitted to the data. The assumption of proportional hazards was formally tested and the partial residuals defined for the Cox proportional hazards regression model were plotted against time.[15] If this assumption was not satisfied, the piecewise Cox model was used. If a treatment by centre interaction was statistically significant at the $p<0.100$ level, the source of the interaction was investigated further and the validity of the proportional hazards assumption confirmed by subsequent analyses. The GMFM score at each time point was analysed by ANCOVA on the overall and goal total scores. Subjective functional assessment of change in gait and global assessment of efficacy were analysed by logistic regression.

A patient-specific approach was adopted to account for missing MPAD data. A linear extrapolation technique was used for observations outside the range of non-missing values and a linear interpolation technique was used for observations inside the range of non-missing values. Unrealistic values (defined as less than –10°) from the linear extrapolation and interpolation techniques were defaulted to –10°. Similarly, missing MPAD data for patients with no on-treatment values were defaulted to –10°. Missing efficacy data for GMFM assessments were accounted for by using a last-observation-carried-forward (LOCF) technique. For missing data on the subjective functional assessment of change in gait, values were defaulted to a 'worse' response.

Statistical analyses with the Fisher's exact test using a 95% confidence interval (CI) were performed to compare treatment groups with respect to the overall incidence of any adverse events occurring in more than 5% of participants in either group.

RESULTS

Participants

In total, 214 participants were randomized to the 4-monthly (n=110) or the yearly (n=104) regimen and were included in the intention-to-treat and safety analyses (Czech Republic n=69, France n=1, Italy n=3, Poland n=98, Slovak Republic n=17, Spain n=24, and UK n=2). In both groups, 83% of participants completed the study. Figure 1 shows participant numbers and reasons for withdrawal. Key demographics and disease characteristics were well balanced between the groups and there was no evidence of a difference between the groups in the use of supportive devices or concomitant physiotherapy or medication (Table I). The median baseline values for MPAD data were at the lower end of the range. Although the normal distribution for MPAD data is unknown, the data were what would be expected to be seen in the clinic, and no patient failed to meet the inclusion criterion of a minimum 10° passive ankle dorsiflexion.

Efficacy

At month 28, 4 months after the last BoNT-A injection, median MPAD for the worse leg (primary endpoint) was 12.00° in the 4-monthly group and 11.00° in the yearly group in the intention-to-treat (Fig. 2) and per-protocol populations. The difference in median MPAD between the groups in the intention-to-treat population was 1.67° (p=0.055 for 4-monthly vs yearly regimen; 95% CI 0.00, 3.41; Fig. 2a). A similar difference in median MPAD (1.59°) was seen in the per-protocol population at month 28 (p=0.065; 95% CI 0.00, 3.46). Median MPAD tended to be greater for the 4-monthly group than for the yearly group from month 8 onwards but this difference did not exceed 1.67° and statistical significance was not reached at any time point in the intention-to-treat population (Fig. 2a). Mean change from baseline in MPAD showed an improvement from month 8 onwards (Fig. 2b). Standard deviations (which indicate the variability of measurements around the means) were similar in both treatment groups, suggesting that there was no difference between the treatment groups that was not reflected in the median values.

Ten participants (9%) in the 4-monthly group and seven (7%) in the yearly group developed fixed contractures of the ankle during the study. A Cox proportional hazards regression model consisting of treatment and centre was fitted to the data. The assumption was confirmed by a Kaplan–Meier plot, which showed that the two estimated survivor functions for each group did not cross (Fig. 3). Although time to development of fixed contractures was shorter in the 4-monthly group than in the yearly group, the difference was not significant (p=0.533; hazard ratio 0.734; 95% CI 0.28, 1.94). Eight participants (7%) in the 4-monthly group and four (4%) in the yearly group were referred for surgery to correct fixed contractures during the study. Time to referral for surgery to correct fixed contractures was shorter in the 4-monthly group than in the yearly group but the difference was not significant (p=0.156; hazard ratio 0.381; 95% CI 0.10, 1.45).

In both groups, although GMFM improved throughout the study, neither the overall nor the goal total scores (Fig. 4) were significantly different between groups. The 4-monthly group had a lower GMFM total score at baseline (75.9) than the yearly group (77.9) but, with time, the

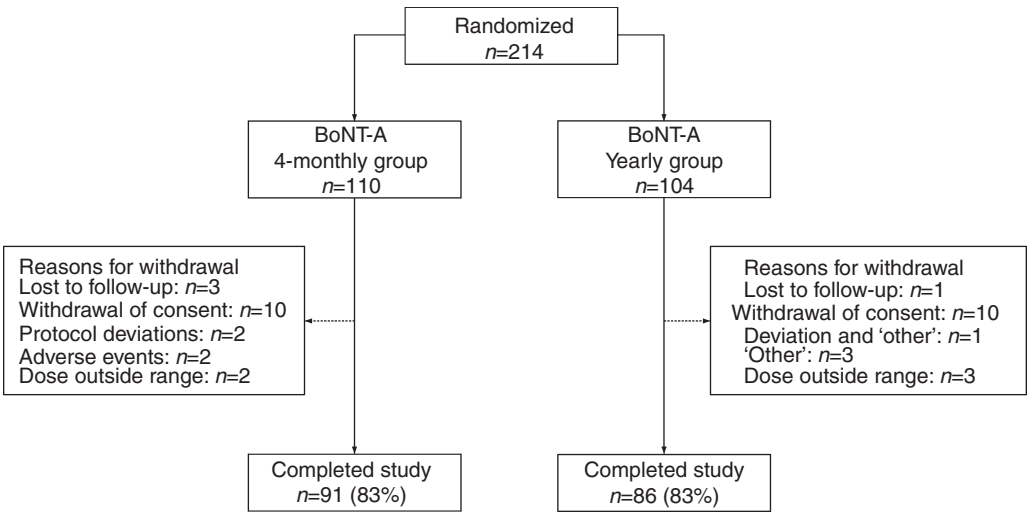


Figure 1: Patient disposition (intention-to-treat population). BoNT-A, botulinum toxin A.

Table I: Baseline patient demographics and disease characteristics (intention-to-treat population)

Parameter	Botulinum toxin type A treatment group	
	4-monthly (*n*=110)	Yearly (*n*=104)
Age, y		
Mean (SD)	3y 8mo (1y 6mo)	4y 4mo (1y 6mo)
Range	1–8y	2–8y
Sex, *n*		
Female	71	57
Male	39	47
Race, *n* (%)		
White	110 (100)	104 (100)
MPAD, median (range)		
Better leg	15.00° (10.00–33.00°)	15.33° (10.00–32.67°)
Worse leg	11.67° (9.67–24.00°)	11.67° (10.00–22.33°)
GMFM, median (range)	75.9 (16.8–98.6)	77.9 (10.0–100.0)
Use of aids and orthoses, *n* (%)	48 (44)	44 (42)
Physiotherapy, *n* (%)		
Continued during study	80 (73)	67 (64)
Stopped before study	23 (21)	36 (35)
Other medications for CP, *n* (%)		
Continued during study	16 (15)	13 (13)
Stopped before study	13 (12)	22 (21)
Age at diagnosis, mean (SD)	13.2mo (10.4)	15.4mo (12.8)

difference between groups diminished. This finding is supported by the median change from baseline in GMFM overall score at month 28, which was greater in the 4-monthly group (8.6) than in the yearly group (5.9). A similar, non-significant difference between the groups was seen for GMFM goal total score; the median change from baseline was slightly higher in the 4-monthly group (12.3) than in the yearly group (9.0).

For the subjective functional assessment of change in gait, measured at months 1, 13, and 25, a majority of participants (55–69%) in the 4-monthly group had response to treatment graded as good, regardless of whether assessment was made by the blinded assessor or the parent or guardian (Figure S1; supporting information, published online). A large proportion of participants (42–63%) in the yearly group also had a response to treatment graded as good by the blinded assessor or the parent or guardian (Figure S1). At month 25, participants in the 4-monthly group were significantly more likely than those in the yearly group to have better responses on the subjective functional assessment of change in gait for assessments made by the blinded assessor (p=0.034; odds ratio [OR] 1.820; 95% CI 1.046, 3.167) or the parent or guardian (p=0.031; OR 1.840; 95% CI 1.059, 3.197; Figures S1c and S1f).

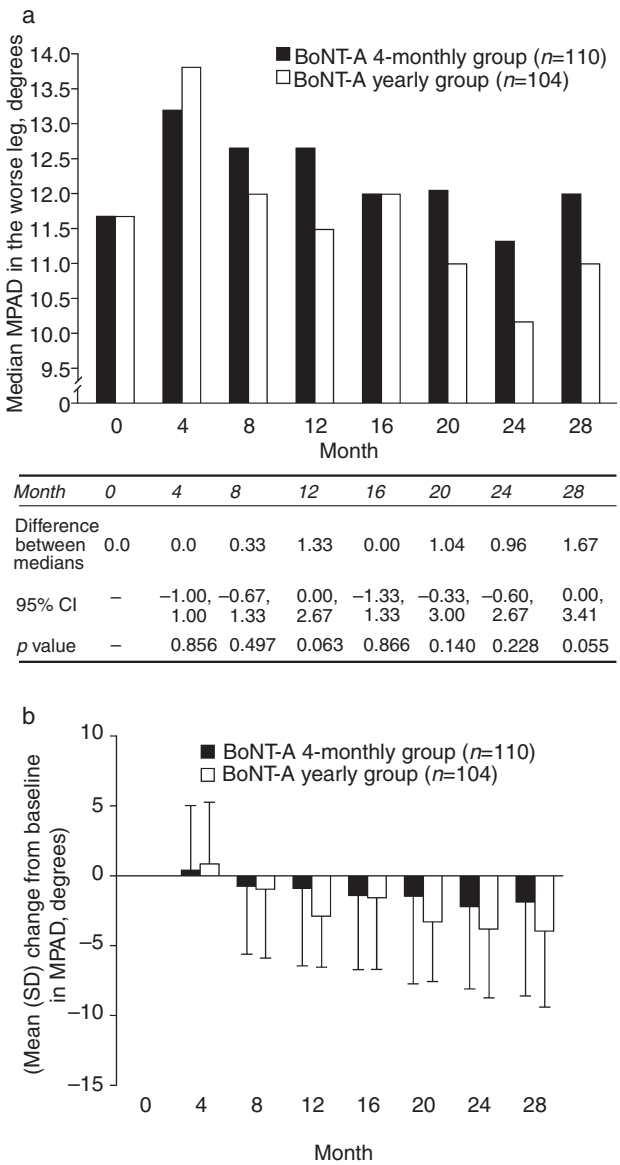
Safety

Adverse events were reported in 89 participants (81%) in the 4-monthly group and 88 participants (85%) in the yearly group (Table II). The majority of adverse events were mild or moderate in severity in the 4-monthly group (71% and 45% respectively) and the yearly group (72% and 56% respectively). Across both groups, the most common adverse events were of the respiratory system (Table II). The incidence of weakness was the same for each group (14%), with the majority of cases being lower-limb or leg weakness.

The two groups were balanced with respect to the number of events and incidence of adverse events, except for convulsions, which occurred in six participants (5%) in the 4-monthly group and 14 (13%) in the yearly group (p=0.044). None of these episodes was considered related to treatment by the investigator. Four of the six participants in the 4-monthly group and 10 of the 14 participants in the yearly group who experienced convulsions had a history of epilepsy, epileptic syndrome, partial epilepsy, or febrile convulsions at baseline.

Neutralizing status

At baseline, neutralizing antibodies were present in one participant in each group. At month 28, neutralizing antibodies were detected in only five participants (5%) in the 4-monthly



Month	0	4	8	12	16	20	24	28
Difference between medians	0.0	0.0	0.33	1.33	0.00	1.04	0.96	1.67
95% CI	–	–1.00, 1.00	–0.67, 1.33	0.00, 2.67	–1.33, 1.33	–0.33, 3.00	–0.60, 2.67	0.00, 3.41
p value	–	0.856	0.497	0.063	0.866	0.140	0.228	0.055

Figure 2: Maximum passive ankle dorsiflexion (MPAD) in the worse leg at each time point in the intention-to-treat population (missing data imputed): (a) median values; (b) change from baseline in mean (SD) values. BoNT-A, botulinum toxin A; CI, confidence interval.

group and two participants (2%) in the yearly group. In the 4-monthly group, the level of neutralizing antibodies was classified as low in one participant and low–intermediate in three participants. One patient in this group was classified with a high level of neutralizing antibodies at the end of the study; the patient did not develop fixed contractures before month 28 and both the physician and parent/guardian graded the global assessment of efficacy as improved. In the yearly group, the level of neutralizing antibodies was low in one patient and low–intermediate in the other.

DISCUSSION

This study showed that for the primary endpoint, median MPAD at month 28, there was no statistically significant difference between 4-monthly and yearly BoNT-A treatment groups. However, there was a treatment difference of 1.67° in favour of the participants treated every 4 months over those treated annually. Although this difference was not statistically significant, the study was designed to detect a difference in MPAD of at least 5°, which was considered to be of clinical relevance and to represent a clinically meaningful improvement in functional gain. The time course for the development of contractures for patients with CP and limb spasticity is unclear and differs among patients, so we would not have expected all of our patients to have developed detectable contractures over the length of the study. In contrast to what would be expected in untreated children with spasticity, however, deterioration in MPAD did not occur in either group. This assertion is supported by the observation that passive ankle dorsiflexion worsens over periods as short as 1 to 3 months in placebo groups of studies that have used this measure.[10,11] In one study, passive ankle dorsiflexion worsened although placebo patients were receiving conventional treatment with physiotherapy and foot orthoses, both before and during the study.[11] Indeed, further research is required to determine the impact of physiotherapy on impairment, function, and disability.[16] A variety of disease measures deteriorate over time in children with spastic CP: ambulatory ability tends to diminish,[17] stride frequency decreases,[18] and the proportion of children requiring orthopaedic surgery increases.[19,20] Our study provides evidence supporting long-term treatment with BoNT-A for lower-limb spasticity in children with CP. Lack of deterioration in MPAD over time also suggests that fewer children will require surgical intervention.

In addition to the median MPAD values, GMFM overall and goal total scores were not significantly different between groups at any time point. The steady increase in overall mobility, indicated by improvements in GMFM scores, does not necessarily equate to reduced spasticity because such scores are expected to increase with age.

In contrast to the objective assessments, subjective assessments demonstrated a statistically significant difference in favour of treating patients every 4 months with BoNT-A over once yearly. The lack of a significant change in MPAD, but not subjective assessment of change in gait, may be explained by the timing of assessments. Each of the MPAD assessments occurred 4 months after the previous BoNT-A injection, whereas the subjective functional assessment of change in gait was performed 1 month after the previous injection. As the peak effect of BoNT-A

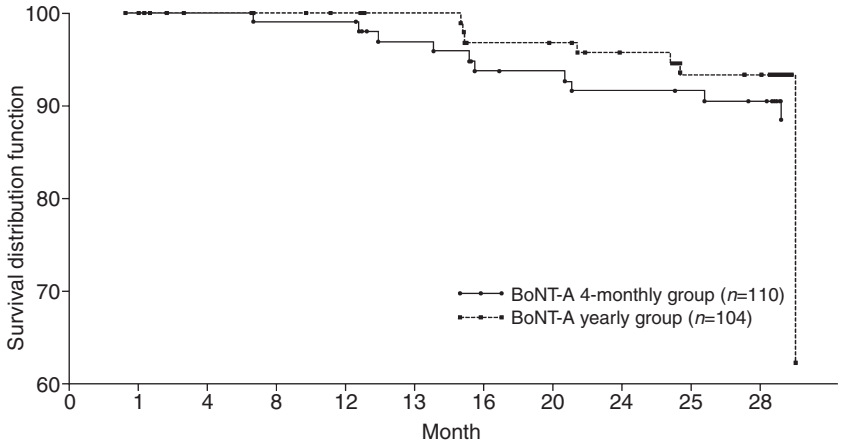
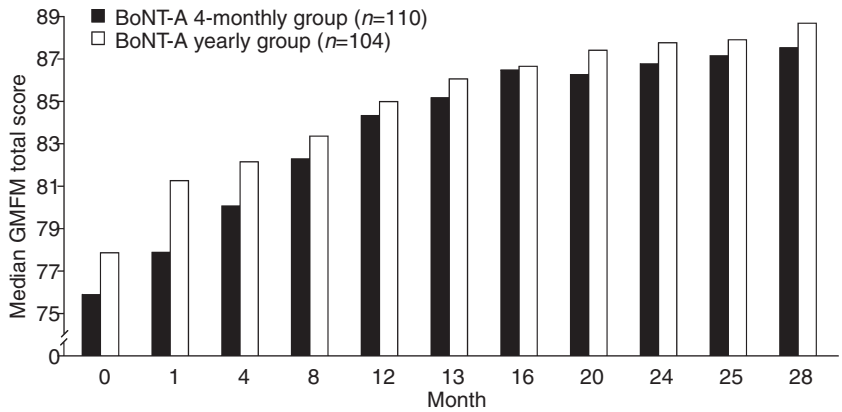


Figure 3: Time to development of fixed contractures. BoNT-A, botulinum toxin A.



Month	*0*	*1*	*4*	*8*	*12*	*13*	*16*	*20*	*24*	*25*	*28*
Difference between medians	–[a]	–2.2	–1.6	–1.4	–0.8	–0.6	–0.8	–0.8	–0.6	–0.6	–0.8
95% CI	–	–6.4, 2.0	–5.6, 2.2	–5.0, 2.2	–4.1, 2.6	–4.2, 2.6	–4.0, 2.4	–3.8, 2.4	–3.4, 2.4	–3.6, 2.2	–3.4, 1.8
p value	–	0.281	0.376	0.406	0.640	0.646	0.582	0.611	0.679	0.566	0.549

[a]The difference between median GMFM total scores at baseline was not calculated

Figure 4: Median Gross Motor Function Measure (GMFM) total score at each time point in the intention-to-treat population (last observation carried forward). BoNT-A, botulinum toxin A; CI, confidence interval.

chemodenervation occurs approximately 3 to 4 weeks after injection,[21] it is unsurprising that between-group difference in MPAD had dropped to a level below significance 4 months after injection. We therefore recommend that assessments of efficacy be performed within 2 months of injection in future studies of BoNT-A.

The incidence and nature of the adverse events seen during this long-term study are consistent with the known safety profile of BoNT-A and with the disease, age, and, medical history of the patient group. Moreover, the majority of treatment-related adverse events were mild to moderate in severity. Importantly, there was no difference in the number of treatment-related events or in the number of patients reporting any treatment-related adverse event between the 4-monthly and yearly treatment groups. Of note, only 7 and 4% of patients in the 4-month and yearly groups respectively, were referred for surgery during the 28-month study. This finding is in line with a Swedish population-based study, which showed that the introduction of new techniques (BoNT-A, selective dorsal

Table II. Summary of all adverse events by severity and the most frequently reported adverse events (affecting >10% of patients; safety population)

	Number of patients (%) with adverse events	
Preferred term	4-monthly group (*n*=110)	Yearly group (*n*=104)
All adverse events	89 (81)	88 (85)
Mild	78 (71)	75 (72)
Moderate	49 (45)	58 (56)
Severe	5 (5)	10 (10)
Pharyngitis	40 (36)	41 (39)
Rhinitis	32 (29)	34 (33)
Bronchitis	34 (31)	31 (30)
Viral infection	22 (20)	28 (27)
Pain	19 (17)	22 (21)
Infection	17 (15)	18 (17)
Weakness	15 (14)	15 (14)
Cough increased	15 (14)	11 (11)
Surgical intervention	12 (11)	13 (13)
Fever	13 (12)	9 (9)
Convulsions[a]	6 (5)	14 (13)

[a]Difference between groups, p=0.044.

rhizotomy, or intrathecal baclofen) to reduce spasticity and dystonia in children with CP resulted in a significant reduction (from 40 to 15%) in the proportion of children undergoing orthopaedic surgery for contracture or skeletal deformity (p=0.002).[20] A retrospective review of 424 children with CP showed that BoNT-A treatment delayed the need for surgery and reduced the frequency of surgical procedures (p<0.001).[22] The investigators found that the prevalence of orthopaedic surgical procedures was significantly lower in patients who received BoNT-A treatment and underwent gait analysis than in patients who were managed according to best-practice guidelines in orthopaedics. Therefore, these and other studies indicate that BoNT-A could play a key role in delaying the need for orthopaedic surgery.[20,22–24]

In our study, neutralizing antibodies were detected in two patients at baseline and in seven patients at month 28. Hence, in total, only five patients (2%) developed neutralizing antibodies over the 2-year study and, in all but one patient, the levels of neutralizing antibodies were low or low–intermediate. The single patient with a high neutralizing-antibody status at the end of the study had a good clinical response. Studies of BoNT-A in other therapeutic indications have shown similar low incidences of neutralizing antibodies.[25] Even if, as previously asserted, neutralizing antibodies may account for non-response to BoNT-A treatment in up to 15% of patients with CP,[26] this does not seem of great clinical concern given the very low incidence and low levels of neutralizing antibodies in both groups after BoNT-A treatment in the current study. Although the total number of patients with neutralizing antibodies at month 28 suggested that neutralizing antibodies developed with more frequent dosing, the data were not analysed statistically and the low patient numbers render the results inconclusive.

Analysis of the data from our study is limited by the lack of a placebo or non-interventional control, which would not have been considered ethical in this population of young children. Nevertheless, assessments were undertaken by an assessor who was blinded to treatment, which minimized the potential bias. We did not apply an adjustment to keep the significance level at the 0.05 level when we analysed multiple comparisons, such as the eight between-group MPAD comparisons. Therefore, the significance level may potentially have been too high. As these data were not statistically significant, however, this did not affect interpretation of the results.

Our assessment of change in gait was also limited as there are no internationally recognized and validated scales. However, we used a simple, subjective evaluation of change in gait from baseline to either the end of the study or withdrawal. These measurements were made by the blinded physician or physiotherapist or by the child's parent or guardian and were intended to provide an impression of gait by someone who knew the child well. For more objective assessments in the future, a fully validated scale is required. In addition, it may have been helpful to document functional gain using video-supported gait scores or instrumental gait analysis.

The statistical analysis for the study included using an LOCF approach for missing data on some endpoints. This was considered a usable and acceptable method when the study was initially planned and is often regarded as a conservative approach for handling missing data. However, LOCF is now becoming less acceptable, and alternative ways for analysing data may be considered in future studies.[27]

Although our study evaluated more than 200 children with limb spasticity in CP, further, larger studies with a more defined patient population would be helpful to confirm our results. It may also be valuable to study individualized rather than fixed injection schemes. The difference between groups for the primary efficacy endpoint was non-significant in our study, although our results favour, but not in a statistically significant way, a greater improvement in objective assessments (time to development of fixed contractures, time to referral for surgery to correct fixed contractures, and GMFM) and significant benefits in

subjective functional assessment of change in gait when children were treated every 4 months rather than yearly. The additional financial, practical, and emotional burden of more frequent injections needs balancing against the magnitude of the improvements.

CONCLUSION

In summary, deterioration of MPAD may be prevented by BoNT-A injections to the gastrocnemius muscles of children with diplegic CP, with a safety profile that is typical of that seen in other indications. Given the specific characteristics of the study population, we were unable to identify which injection schedule was preferable. Importantly, however, the safety profiles of the two injection regimens were similar.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article:

Figure S1: Subjective functional assessment of change in gait in the intention-to-treat population graded by the blinded assessor at (a) month 1, (b) month 13, and (c) month 25, and graded by the parent/guardian at (d) month 1, (e) month 13, and (f) month 25. BoNT-A, botulinum toxin A; CI, confidence interval; OR, odds ratio. Worse indicates worse than baseline.

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CONFLICT OF INTEREST

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