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Original Article

Long-Term Evaluation of Low-Dose Betamethasone for Ataxia Telangiectasia

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ABSTRACT

Background: Ataxia telangiectasia is an autosomal recessive disorder characterized by cerebellar ataxia, telangiectases, immune defects, and a predisposition to malignancy. Quality of life is severely impaired by neurological symptoms. However, curative options for the neurological symptoms are limited. Recent studies have demonstrated short-term improvement in neurological symptoms with betamethasone therapy. However, the long-term and adverse effects of betamethasone are unclear. The aim of this study was to evaluate the long-term effects, benefits, and adverse effects of low-dose betamethasone in ataxia telangiectasia.

Methods: Six patients with ataxia telangiectasia received betamethasone at 0.02 mg/kg/day for two years. After cessation of betamethasone, the patients were observed for two additional years. Neurological assessments were performed, and adverse effects were monitored every three months throughout the four-year study period.

Results: Transient improvement of neurological symptom was observed in five of the six patients. However, after two years betamethasone treatment, only one of the six patients showed a slight improvement in the neurological score, one patient showed no change, and the neurological scores of the remaining four patients deteriorated. After the cessation of betamethasone treatment, neurological symptoms worsened in all patients. As an adverse effect of betamethasone, transient adrenal dysfunction was observed in all cases.

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Ethical approval: The protocol was approved by the Institutional Review Boards (IRBs) of each participating institution. Informed consent or assent for participation in this clinical trial was obtained from all parents in accordance with the Declaration of Helsinki.

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Conclusions: Although these findings are in agreement with previous studies suggesting that short-term betamethasone treatment transiently benefits patients with ataxia telangiectasia, the long-term benefits and risks should be carefully considered.

Introduction

Ataxia telangiectasia (A-T) is an autosomal recessive disorder characterized by cerebellar ataxia, telangiectases, immune defects, and a predisposition to malignancy. In 2006, a child's parents noticed that their son's neurological signs improved when he was occasionally given betamethasone to treat asthmatic bronchitis attack.[1] Based on this observation, an extended clinical study was performed using oral betamethasone at a dose of 0.1 mg/kg/day for 10 days. Six patients were enrolled, and five of the six patients exhibited a clear increase in neurological performance.[2] Oral betamethasone at a dose of 0.1 mg/kg/day was also confirmed to be effective in a randomized study.[3] To reduce the risk of adverse effects (AE) of betamethasone treatment, several additional clinical studies were performed using low-dose betamethasone (0.01 to 0.03 mg/kg), and effectiveness was observed.[4–6] To reduce steroid-related side effects, researchers have also focused on innovating the method of drug delivery. Encapsulation of dexamethasone sodium phosphate into autologous erythrocytes (EryDex), which allowed for the slow release of dexamethasone for up to one month after dosing, resulted in significant improvement in neurological symptoms without the typical side effects associated with steroid administration.[7,8] However, to conduct an EryDex trial, special equipment is required. Therefore the aim of our study was to evaluate the long-term efficacy and safety of low-dose oral betamethasone, which is more available in patients with A-T.

Methods

Study design and patient selection

This study is a phase II, multicenter, single-arm, non-random, open-label trial. The trial was registered with the University Hospitals Medical Information Network Clinical Trials Registry (UMIN-CTR; UMIN000004109). The Institutional Review Board approval number is 2016-1001.

Primary outcome

The primary outcome is improvement of ataxia evaluated by neurological scales.

Secondary outcome

The secondary outcome is monitoring of AEs related to steroid use, such as glucose intolerance, decreased adrenal function, decreased immunological status, increased frequency of cancer development, and changes in urinary oxidation markers.

Eligibility criteria

Patients with A-T who met the eligibility criteria below were enrolled in the study.

Inclusion criteria

Patients must meet all of the following key inclusion criteria:

1. A diagnosis of A-T
2. Age less than 20 years
3. Performance status using the Eastern Cooperative Oncology Group 0 to 2
4. National Cancer Institute Common Toxicity Criteria $\leq$ Grade I
5. Informed consent obtained from a parent or guardian. Participants older than 16 years could provide consent themselves if they were able to communicate.

Exclusion criteria

Patients were excluded from the enrollment if they met any of the following criteria:

1. Infection
2. Serious complications of major organs
3. Malignancy
4. Patients who are judged inadequate by the investigator
5. Participation in any clinical trial within the past three months

Study protocol

Each patient received betamethasone orally over a four-week cycle; this comprised 14 days of administration (0.02 mg/kg/day) followed by a 14-day washout period for two years. An oral-based questionnaire showed that adherence to betamethasone treatment was almost 100%.

Neurological assessment

Neurological assessment was performed every three months using the Scale for the Assessment and Rating of Ataxia (SARA)[9] and the A-T Neurological Examination Scale Toolkit (AT-NEST)[10] by two experts in pediatric neurology. Neurological imaging using magnetic resonance imaging was performed before the trial and once a year thereafter. Electroencephalography, auditory brainstem response, visual evoked potential, and peripheral nerve conduction were monitored during the trial period. Intelligence quotient (IQ) was measured using Wechsler Intelligence Scale for Children IV. An otolaryngologist evaluated dysphagia once per year.

Measurement of clinical indicators

Detailed measurements of clinical indicators are provided in Supplementary Data 1. Cancer was monitored by performing routine physical examinations, complete blood cell counts, and tests for serum tumor markers.

Measurement of urinary oxidative stress biomarkers and total antioxidant capacity

Detailed measurements of clinical indicators are provided in Supplementary Data 2.

Statistical analysis

The primary analysis used the intent-to-treat principle. Parametric unpaired analyses were performed using the Student *t* test. Parametric paired analyses were performed using the paired Student *t* test. Differences in mean scores were analyzed using repeated measures analysis of variance. Posthoc tests using the Bonferroni correction were also performed. All statistical tests were two-sided, and a *P* value less than 0.05 was considered statistically significant.

Results

Enrolled patients

Supplementary Table 1 summarizes clinical information from the six enrolled patients. The mean age at enrollment was 9.2 (range, six to 12). There were three males and three females. All patients had classical A-T with *ATM* null mutations. A pre-enrollment evaluation was not performed on patient AT06. Consent for patient AT02 was withdrawn one year after initiation of the trial, as the child's parents did not feel there was any benefit.

Neurological assessment

All patient data

The average scores of all patients were analyzed (Figs 1A and B). An increase in the SARA score and a decrease in the AT-NEST score indicate deterioration of neurological status. The only statistically significant change during betamethasone administration was observed in the SARA score at the six-month observation point, which decreased from 18.8 at baseline to 17 ($P = 0.0327$, paired *t* test) at six months. Although it did not reach statistical significance, the average AT-NEST score increased from 63.0 at baseline to 67.2 at six months ($P = 0.777$ paired *t* test). There was no significant change in either SARA score or AT-NEST score at 12 or 24 months.

The delta score (Δ score) was calculated as the post-treatment value minus the pretreatment value for each patient. Using the SARA scale, the delta score increases when the score worsens, whereas using the AT-NEST scale, the delta score decreases when the score worsens. The average delta scores of all patients were analyzed. The changes of delta scores between zero to six months or zero to 12 months (during betamethasone administration) and 24 to 48 months (after cessation of betamethasone administration) was significantly increased in the SARA scale. The changes of delta scores between zero to three months or zero to six months (during betamethasone administration) and 24 to 48 months (after cessation of betamethasone) was significantly decreased in the AT-NEST scale. These results indicate a worsening of the delta score. The differences were statistically significant (Figs 1C and D).

Next, individual parameters that comprise the SARA and AT-NEST scores were analyzed (Table 1 and Supplementary Figures 1 and 2). Improvement of gait after betamethasone treatment was a statistically significant influence for the SARA score ($P = 0.003091$), and improvement of ataxia after betamethasone treatment was a statistically significant factor influencing the AT-NEST score ($P = 0.006778$).

Individual patient data

For each patient, the net changes in SARA and AT-NEST scores were determined (Fig 2A and B, Supplementary Figure 3). Four patients (AT01, AT03, AT04, and AT05) showed improved delta scores using the SARA scale for the first six months, but only patients AT03 and AT04 still showed improvement at 12 months. At the end of the 24-month trial, compared with the baseline score, the SARA score improved in patient AT04 and stabilized in patient AT05, whereas according to the AT-NEST score, three patients (AT03, AT04, and AT05) showed improved delta scores for the first six months, but only AT04 still showed improvement at the end of the 24-month trial.

After the end of betamethasone treatment, however, the delta score at 24 to 48 months was worse in all cases. There was no correlation between delta scores in the SARA or AT-NEST scale and age (Supplementary Figure 4).

Although only partial improvements in the neurological score were seen using the objective scoring methods, the patients' caregivers did report transient improvements in their neurological status. Decreased involuntary movements and dysarthria and better stability of the trunk during the first six to 12 months of betamethasone treatment were reported in patients AT01, AT03, and AT05 (Table 2).

Neurological imaging

There was no difference in cerebellar atrophy between patients during the observation period, although two of the six patients (AT01 and AT04) showed microbleeding in cerebral white matter during administration of betamethasone (Supplementary Figure 5A and B).

IQ, dysphagia, and electrophysical examination

An abnormal value indicating peripheral neuropathy was observed 12 months after betamethasone administration in three of the six patients in the peripheral nerve conduction study. There were no changes in IQ, dysphagia, electroencephalogram, auditory brainstem response, or visual evoked potential.

Adverse effects

In this clinical trial, all patients reported at least one AE (Table 3). All the patients showed secondary adrenal insufficiency. Diurnal variations in adrenocorticotropic hormone and cortisol were suppressed to below the range of detection, and these two hormones showed only low reaction to corticotrophin-releasing hormone stimulation tests performed 12 months after initiation of betamethasone administration (Supplementary Figure 6). Patient AT03, whose cortisol was the most suppressed, complained of significant fatigue during the washout period and required hydrocortisone replenishment. In addition, two other patients complained of severe fatigue during the washout periods. Therefore the protocol was modified to administer betamethasone every other day (0.02 mg/kg/day) after discussion with the Data and Safety Monitoring Committee and subsequent approval by the Institutional Review Board. Because the total cholesterol level was high in patient AT03 at baseline before enrollment in the trial and further increased after betamethasone administration, the betamethasone dose was reduced to 0.01 mg/kg/day (every other day) for this patient. No patient exhibited acute adrenal crisis. The adrenocorticotropic hormone and cortisol response to corticotrophin-releasing hormone stimulation tests recovered to the normal range 12 months after the end of betamethasone administration in

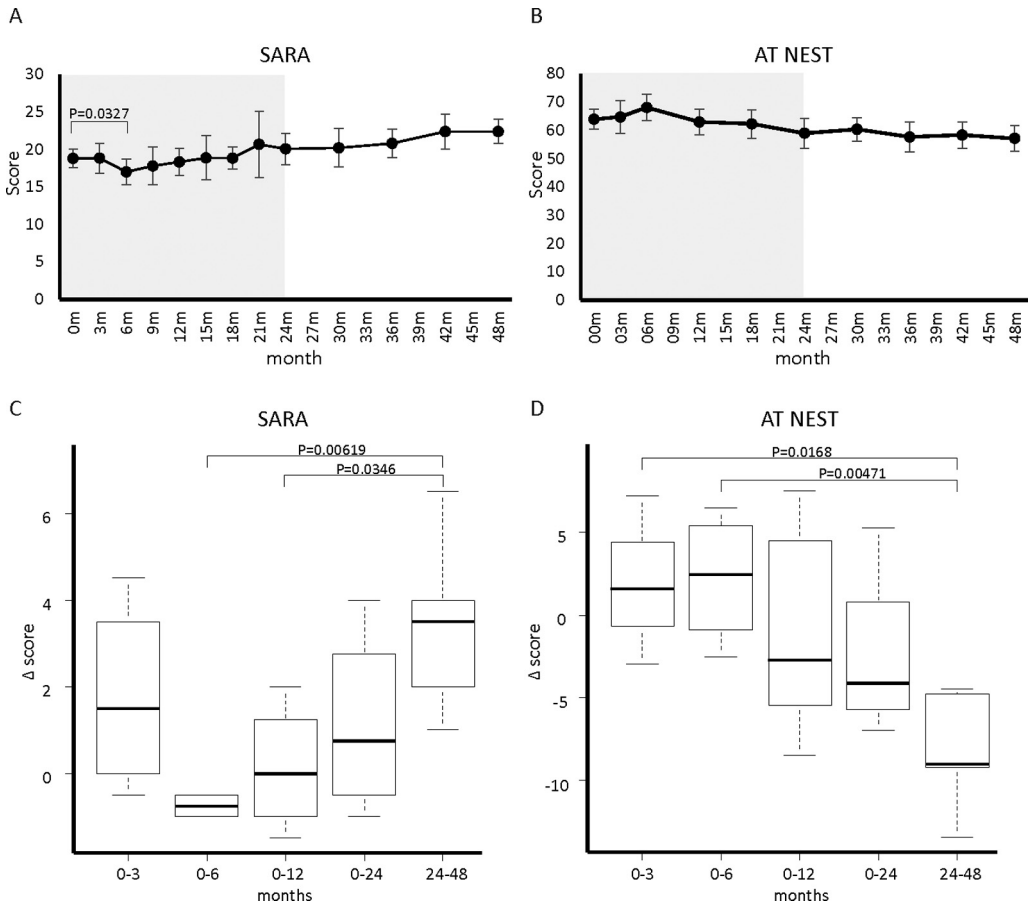

FIGURE 1. Mean SARA (A) and AT-NEST (B) scores during and after betamethasone administration. The gray shaded area indicates the administration of betamethasone. The mean and dispersion of the Δ scores for SARA (C) and AT-NEST (D) were plotted against time using box-and-whisker plots.

all patients. Ocular hypertension and growth suppression were observed in four patients (Supplementary Figure 7). Typical steroid-dependent body changes including weight gain (body mass index, 16.6 to 20.5) were observed in one patient. Glucose intolerance, changes in lipid metabolism, and osteoporosis are also causes for concern during long-term steroid use. Fortunately, the HbA1c level did not change during the trial in any patient. Increased levels of triglycerides were observed in three of the six patients. Serum levels of the *N*-telopeptide of type I collagen, a biomarker for bone absorption, were within normal limit in all patients (Supplementary Figure 8).

Immunosuppression is a major potential AE of steroid use; however, betamethasone administration had no significant effect on immunological parameters or virus reactivation (Supplementary Figure 9, Supplementary Table 2).

Clinical outcome

Patient AT05 developed diffuse large B cell lymphoma 2.5 years after cessation of betamethasone administration.

Analysis of oxidative stress markers and total antioxidant power in patients with A-T

Although antioxidative mechanisms are known to improve cerebellar functions in patients with A-T receiving short-term

TABLE 1.
Statistical Differences in Individual Parameters Comprising the SARA and AT-NEST Scores

SARA	*P*-value	AT-NEST	*P*-value
Gait	0.003091*	Communication	0.767
Stance	0.424133	Eye movements	0.9158
Sitting	0.944996	Ataxia	0.006778*
Speech disturbance	0.4011	Movement disorder	0.7704
Finger chance	0.4865	Power	0.5314
Nose-finger test	0.620965	Neuropathy	0.5431
Fast alternating hand movements	0.8122		
Heel-shin slide	0.891155		

Abbreviations:
ANOVA = Analysis of variance
AT-NEST = A-T Neuro Examination Scale Toolkit
SARA = Scale for the Assessment and Rating of Ataxia
*Statistical significance by repeated measures ANOVA.

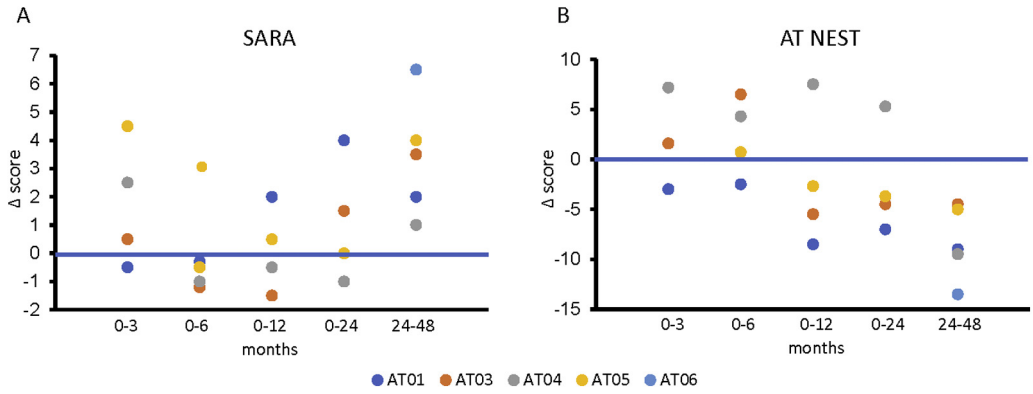

FIGURE 2. The Δ score for SARA (A) and AT-NEST (B) during and after betamethasone administration. Changes in neurological score for each patient are plotted over time.

betamethasone,[11] administration of this steroid had no remarkable effects on oxidative stress measurements in our study (Supplementary Figure 10).

Discussion

Several studies suggest that steroids have a beneficial effect on neurological disability in A-T (Table 4). To reduce steroid-related side effects, the minimum therapeutically effective dose of oral betamethasone was investigated, and low-dose betamethasone was effective at ameliorating neurological symptoms without obvious AEs in A-T.[4,6] So far, eight clinical trials using steroids in A-T have been reported, one of which was a randomized crossover trial.[3] EryDex was administered in two of these trials, and evaluated for 24 and 30 months. However, in an oral low-dose betamethasone trial, the efficacy of steroid treatment was evaluated within a relatively short time period. Only one recent study evaluated patients for 240 days.[6] This study design involved 60 days of treatment at an extremely low steroid dose, as well as tapering and washout periods. The mechanism through which low-dose betamethasone exerts beneficial therapeutic effects in A-T and the risk of AE development from long-term administration have not been elucidated. Our study included two years of long-term steroid administration and a follow-up period of two years. Steroid administration partially improved neurological impairment at early time points. However, this study demonstrates that neurological impairment, as determined by SARA and AT-NEST tests, gradually worsened despite continuing therapy with low-dose betamethasone. In only one patient (AT04), neurological scores were slightly improved by administration of low-dose betamethasone. Although our study suggests that low-dose oral betamethasone therapy may delay the progression of neurological deterioration, these results clearly demonstrate that steroid administration does not halt the progression of neurological deterioration. A functional magnetic resonance imaging study suggested that betamethasone administration may improve motor performance by facilitating cortical compensatory mechanisms.[5] Betamethasone may improve neurological symptoms via cortical compensatory mechanisms but could not attenuate neurological degeneration. We also analyzed the effect of betamethasone on specific neurological parameters, and betamethasone resulted in an improvement in ataxic gait. Multiple parts of the central nervous system in addition to the cerebellum are affected in A-T.[12,13] Betamethasone may exert its function on specific neural regions selectively or may only be able to induce cortical compensatory mechanisms for specific lesions.

Our study extensively analyzed the AEs of low-dose betamethasone. Adrenal suppression was observed in all patients, as was expected. These observations strongly suggest that supplementation with glucocorticoids on sick days during low-dose betamethasone therapy is necessary. Fortunately, adrenal function recovered to the normal levels after cessation of low-dose betamethasone. However, it should be noted that adrenal insufficiency after discontinuation of glucocorticoid occurs frequently.[14] Growth retardation was unexpectedly observed in four of the six patients, another serious AE of low-dose betamethasone. In our study, no changes in lymphocyte numbers were observed. In addition, the level of total immunoglobulin was not altered, and no severe infections occurred. Thus the effect of low-dose betamethasone on immunological function appears to be minimal. However, reactivation of the herpes virus was observed in some individuals during the trial. Careful monitoring for viruses is required during betamethasone therapy. In the imaging study, a microhemorrhage in white matter was observed, which we suggest was caused by disease progression. However, it is difficult to neglect the potential AEs of betamethasone treatment.

Our trial has several limitations. Although single-arm trials are helpful in obtaining preliminary evidence of the efficacy of a treatment and in collecting safety data, they cannot be generally used to confirm the efficacy of a treatment. In addition, the interpretation of trial results can be complicated by the inability to distinguish among the effect of the treatment, a placebo effect, and the changes in the natural progression of the disease. Another concern that single-arm trials face is the challenge of selecting appropriate endpoints that are sensitive or specific enough to demonstrate clinical impact in the absence of direct comparison data. Although AT-NEST and SARA are valuable resources for the semiquantitative evaluation of clinical progression, they are limited with regard to sensitivity and specificity, and are particularly prone to inter-rater variability.

Several other studies have reported more pronounced improvements over relatively short time periods; our study partially

TABLE 2.
Caregiver-Reported Improvement in Neurological Symptoms

Preferred Term	Number (%) of Caregivers
Any benefits	4 (66)
Improvement of trunk stability	3 (50)
Improvement of involuntary movement	1 (16)
Improvement of dysarthria	1 (16)
Improvement of walking	1 (16)

The number (%) of caregivers sorted by decreasing frequency of reported events.

TABLE 3.
Adverse Effects

AE	Number (%) of Patients
Any AE	18*
Ocular hypertension	4 (66)
Growth suppression	4 (66)
Moon face	3 (50)
Fatigue and asthenia	3 (50)
Body weight gain	2 (33)
Hypertrichosis	1 (16)
Hyperphagia	1 (16)
Irregularity of menstruation	1 (16)
Pneumococcal pneumonia	1 (16)
Molluscum contagiosum	1 (16)
Labial herpes infection	1 (16)

Abbreviation:
AE = Adverse event
The number (%) of patients reporting AEs sorted by decreasing frequency of events in all patients.
* The total number of any AE in all six enrolled patients.

confirms these results. One of the differences between our study and other studies is the difference in the neurological evaluation method employed. We used AT-NEST and SARA, whereas several other studies used International Cooperative Ataxia Rating Scale for neurological evaluation; these differences may have affected the results.

Age at enrollment may have affected the efficacy of the treatment. One may speculate that the younger patients may have benefited more from low-dose steroid treatment. There was no relationship between age and improvement. However, this should be carefully evaluated because the sample size was too small to draw any firm conclusions and sampling bias may have affected the results. In terms of interindividual disease variability, our results suggest that the neurologically milder phenotype patient (AT04) responded to betamethasone. This suggests that interindividual disease variability affected the response to betamethasone. To clarify this point, a further study should be performed using a group of patients with similar neurological scores, and if possible, an age-matched group of patients.

Our study and previous studies demonstrate that short-term betamethasone treatment transiently results in an improvement in neurological function in patients with A-T. However, from the standpoint of the long-term benefits and the risk of AEs, the utility of betamethasone seems to be limited. Although new drug delivery systems to avoid the risk of AEs, such as EryDex, could be an attractive approach for A-T, the benefit-to-risk ratio should be carefully determined over both the short and long terms.

TABLE 4.
Literature Review of Steroid Administration for A-T

Number of Patients	Drug/Route	Dose and Method	Duration	Efficacy	Country	Ref.
1	BETA mPSL	First cycle: 0.1 mg/kg/day b.i.d. q12H Second cycle: 2 mg/kg/day b.i.d. q12H	4 weeks 4 weeks	Improvement was dramatic No beneficial effect	Italy	1
6	BETA po	0.1 mg/kg/day b.i.d. q12H	7 days	5 of the 6 patients exhibited a clear amelioration of the neurological performance	Italy	2
6	BETA po	First cycle: 0.01 mg/kg/day Second cycle: 0.03 mg/kg/day	20 days followed by 20 days washout 20 days followed by 20 days washout Total 80 days	0.01 mg/kg; efficacy is limited 0.03 mg/kg; significant improvement in all patients	Italy	4
13	BETA po	First cycle: 0.1 mg/kg/day b.i.d. q12H Second cycle: tapered dose* Third cycle: 0.1 mg/kg/day b.i.d. q12H	30 days 30 days 30 days (tapering and washout) Total 120 days	Improvement: 28% (ITT) and 31% (PP)	Italy	3
4	BETA po	0.03 mg/kg/day	Not described	Improved in all patients	Italy	5
7	BETA po	First cycle: 0.001 mg/kg/day Second cycle:0.005 mg/kg/day Third cycle: 0.01 mg/kg/day	60 days 60 days 60 days 60 days (tapering and washout) Total 240 days	0.001 mg/kg 0.005 mg/kg; 4 of 9 patients had a benefit 0.01 mg/kg; 5 of 9 patients had a benefit	Italy	6
22	DEX EryDex		6 months	Improvement: 22/22 (ITT) and 18/22 (PP)	Italy	7
4†	DEX EryDex		24 months	Improvement: 4/4	Italy	8

Abbreviations:
BETA = Betamethasone
b.i.d. = Bis in die
DEX = Dexamethasone
EryDEX = Intraerythrocyte infusion of dexamethasone
ITT = Intent to treat
mPSL = Methylprednisolone
po = Per oral
PP = Per protocol
q12H = Every 12 hours
* For 4 days, three-quarters of the maximum daily dose (0.075 mg/kg/day); for 4 days, half the maximum daily dose (0.050 mg/kg/day); and for 2 days, one-quarter of the maximum daily dose (0.025 mg/kg/day)
† These patients were continuously enrolled from the previous EryDEX trial.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pediatrneurol.2019.05.006.

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