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RESEARCH ARTICLE

Clobazam versus corticosteroid for developmental and epileptic encephalopathy with spike–wave activation in sleep ((D)EE-SWAS): Results of a multicenter observational study

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Abstract

Objective: Developmental and epileptic encephalopathy with spike–wave activation in sleep ((D)EE-SWAS) is associated with acquired cognitive and behavioral deficits. This international multicenter study aimed to compare cognitive and safety outcomes following initial treatment with corticosteroid and clobazam in patients not eligible for the Randomized European trial of Steroids versus Clobazam Usage for Encephalopathy with Electrical Status Epilepticus in Sleep (RESCUE ESES).

Methods: Ten centers participated in this retrospective study. Inclusion criteria were diagnosis of (D)EE-SWAS between 2 and 12 years of age; treatment with either clobazam or corticosteroid for a consecutive period of more than 1 month within 1 year of diagnosis; and no prior treatment with clobazam or corticosteroid. Primary outcome was defined as improvement in daily functioning after 6 months of treatment, as judged by a principal investigator. Spike–wave index (SWI) was measured as secondary outcome and occurrence of adverse events was assessed. Data were analyzed by an intention-to-treat principle. In addition, an as-treated analysis was conducted to compare outcomes between patients who received oral prednisolone and intravenous methylprednisolone at any point during the 6-month treatment course, regardless of their initial selected treatment (corticosteroid or clobazam).

Marleen M. L. van Arnhem and Linde J. Vijn are co-first authors.

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Results: Seventy-two patients met eligibility criteria and were initially treated with corticosteroid ($n = 24$) or clobazam ($n = 48$) between June 2011 and March 2020. Baseline characteristics did not differ between groups. After 6 months, 84% of patients in the corticosteroid group showed improvement in daily functioning, compared to 51% in the clobazam group (relative risk [RR] 1.6, 95% confidence interval [CI] 1.2–1.8, $p = .012$). SWI improved in the corticosteroid group (median change from baseline −10, interquartile range [IQR] −26 to −1), but not in the clobazam group (median change 0, IQR −20 to 7, $p = .036$). Both treatments were well tolerated. In patients treated with corticosteroid, intravenous pulse methylprednisolone therapy was better tolerated than daily oral prednisolone.

Significance: These findings complement the results of the RESCUE ESES trial and are consistent with the superiority of corticosteroid over clobazam in the early management of children with (D)EE-SWAS.

KEYWORDS

(D)EE-SWAS, clobazam, cognition, corticosteroid, ESES

1 | INTRODUCTION

Developmental and epileptic encephalopathy with spike–wave activation in sleep ((D)EE-SWAS) is a rare childhood epilepsy syndrome that is characterized by nearly continuous spike-wave discharges on electroencephalography (EEG) during sleep, accompanied by acquired cognitive and behavioral deficits.[1,2] The syndrome was previously known as electrical status epilepticus in sleep (ESES) or continuous spikes and waves during slow wave sleep (CSWS), both referring to the typical EEG pattern of spike–wave discharges during more than 85% of slow-wave sleep.[3] The International League Against Epilepsy (ILAE) has recently redefined the syndrome to also include atypical cases, such as those with spike–wave discharges for 50%–85% of non–rapid eye movement (NREM) sleep or with significant developmental delay but without arrest or regression.[4] Clinical seizures are often, although not necessarily, part of the syndrome.[5]

(D)EE-SWAS has been associated with specific structural and genetic etiologies, such as thalamic injuries and a spectrum of genetic variants, including *GRIN2A* mutations.[6,7] In many patients, however, the etiology remains unclear.

Although spike–wave activation in sleep and clinical seizures usually resolve spontaneously around puberty, when (D)EE-SWAS is left untreated, cognitive deficits persist in most children.[8] Therefore, the main goal of treatment is to prevent or minimize cognitive impairment. Small observational studies have reported that immunomodulating agents and benzodiazepines are the most effective treatments for children with (D)EE-SWAS,[9,10] with some data suggesting superiority of corticosteroid over clobazam.[11] The quality of the evidence provided by these studies, however, has been poor and treatment choice has been traditionally based on expert opinion or institutional practice. Based on this background, we recently conducted the Randomized European trial of Steroids versus

Key points

- The main goal of treatment in developmental and epileptic encephalopathy with spike–wave activation in sleep (D)EE-SWAS is to prevent or minimize cognitive impairment.
- This multicenter retrospective study suggests the superiority of corticosteroid over clobazam to improve daily functioning.
- Intravenous pulse methylprednisolone therapy was better tolerated than daily oral prednisolone.
- These findings complement the results of the Randomized European trial of Steroids versus Clobazam Usage for Encephalopathy with Electrical Status Epilepticus in Sleep (RESCUE ESES).

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Clobazam Usage for Encephalopathy with Electrical Status Epilepticus in Sleep (RESCUE ESES), to compare cognitive outcomes between corticosteroid and clobazam as initial treatment in children with (D)EE-SWAS. A total of 45 children were enrolled in this multicenter trial, which involved a blinded outcome assessment after 6 months of treatment. Although the trial was terminated prematurely due to feasibility constraints and the target sample size was not met, the results showed that early initiation of corticosteroid is associated with better intelligence quotient (IQ) outcomes compared with clobazam.[12]

The RESCUE ESES provided some evidence for a superior efficacy of steroids in the early management of children with (D)EE-SWAS. However, feasibility problems and strict eligibility criteria prevented inclusion of many patients. In the current observational study, we evaluate the cognitive and safety outcomes after early treatment with corticosteroid and clobazam in patients with (D)EE-SWAS who did not meet all eligibility criteria for RESCUE ESES.

2 | METHODS

2.1 | Patient selection

In this retrospective study, patients were enrolled from center involved in the setup of RESCUE ESES, who were not eligible for the trial due to various reasons (the most common being inability to perform neuropsychological testing before start of treatment, (D)EE-SWAS diagnosis more than 6 months ago, and no consent from parents for trial participation) but in whom treatment was started between June 2011 and March 2020, and administered similarly to patients enrolled in RESCUE ESES. Seven additional patients were selected from an Australian center that was not involved in RESCUE ESES. Eligible patients were diagnosed with (D)EE-SWAS between the ages of 2 and 12 years; were treated with clobazam or corticosteroid within 1 year of the (D)EE-SWAS diagnosis and for more than 30 consecutive days; had received no prior treatment with clobazam or corticosteroid for more than 2 weeks in total before the treatment evaluated in this study; and had outcome data available 6 months (±2 months) after start of treatment. Criteria for (D)EE-SWAS diagnosis were a spike–wave index (SWI) of more than 50% in NREM sleep on EEG in time temporally related to delay, arrest, or regression of development. Table S1 provides a comparison of the inclusion criteria between the RESCUE-ESES and the present study.

2.2 | Data collection

Individual patient data were collected between September 2019 and April 2020. Baseline information was obtained from medical records within 6 months before the start of treatment with clobazam or corticosteroid. Follow-up information was obtained from medical records 6 months (±2 months) after the initiation of clobazam or corticosteroid.

2.3 | Outcomes

The primary outcome, defined prior to conducting the retrospective data extraction and analysis, was improvement in daily functioning, as judged by the principal investigator at each participating center, based on history taking from parents/caregivers that was noted in the medical records. A patient's daily functioning was considered improved if there was progress in one or more domains that led to improved daily living skills (i.e., communication, alertness, resilience, behavior, ability to acquire new skills, fatigability, and social interaction), without clear deterioration in other domains. This subjective outcome measure was chosen because many patients were excluded from the RESCUE ESES because of inability of centers to perform formal neuropsychological assessment immediately before treatment initiation. In a subgroup of patients with available formal neuropsychological assessment, we evaluated as secondary outcomes the IQ responder rate (defined in accordance with RESCUE ESES protocol as the percentage of patients achieving an improvement of 11.25 IQ points or more, i.e., 75% of the standard deviation [SD][12]) and the change in IQ (delta IQ) from baseline to 6 months.

Secondary outcomes were the change in sleep spike–wave index (delta SWI) from baseline to 6 months (delta SWI), the proportion of EEG responders (defined as those with a SWI decrease ≥25%) at 6 months, the proportion of patients with SWI <50% at 6 months, and the proportion of patients with clinical seizures during the 6-month treatment period, and occurrence of adverse events during the treatment period.

EEG outcomes were determined in either a sleep-deprived EEG or a whole-night EEG. SWI was calculated in a selected epoch of 10 min in the first NREM cycle, 5 min after alpha attenuation. The seconds with spike–wave activity in this epoch were counted visually and divided by the total time (600 s) to calculate the SWI. In each EEG, presence or absence of physiological sleep phenomena (sleep spindles, K-complexes, and vertex waves) was assessed.

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We also described proportions of patients who, at the 6-month follow-up, were still on their initially selected treatment, switched to the alternative treatment (from clobazam to corticosteroid, or vice versa), or were receiving combination treatment with both clobazam and corticosteroid, or had stopped any treatment (Figure 1).

2.4 | Statistical analysis

We presented baseline characteristics as mean (SD) or median (interquartile range [IQR]) for continuous data and absolute numbers and proportions for categorical data. The primary and secondary outcomes were analyzed according to the intention-to-treat (ITT) principle, by assessing outcomes according to the initially selected treatment. In addition, an as-treated analysis was conducted to compare the outcomes between patients who received oral prednisolone and those who received pulse intravenous (IV) methylprednisolone at any point during the 6-month treatment course, regardless of their initially selected treatment (meaning that patients who initiated on clobazam but switched to or added corticosteroid during the 6-month period were included in this analysis).

For the primary outcome, logistic regression was used to model differences in daily functioning between the treatment groups, presented as relative risks (RRs) with 95% confidence intervals (CI).[13] For secondary outcomes, categorical measures were analyzed with logistic regression, with differences presented as RRs with 95% CIs. For continuous secondary outcomes, the planned linear regression analysis could not be applied due to violation of the underlying assumptions, and the non-parametric Wilcoxon rank-sum test with continuity correction was used, with results presented as medians with IQRs.

Additional analyses were performed to determine potential prognostic factors for the primary outcome in relation to the initially selected treatment. First, univariable logistic regression was performed to assess the influence of age at (D)EE-SWAS diagnosis, age at seizure onset, baseline IQ, baseline SWI, normal development prior to (D)EE-SWAS, established etiology, number of previous antiseizure medications (ASMs) and presence of magnetic resonance imaging (MRI) abnormalities. Variables with a p-value lower than .3 were included in the multivariable regression analysis, using multiple imputation to handle missing data. For this purpose, five imputed datasets were generated and the results were pooled.

Statistical significance was set at $p < .05$. Analyses were done with the statistical software R, version 4.2.1 and RStudio, version 1.3.1093.

3 | RESULTS

3.1 | Characteristics of patients at baseline and patient disposition

Ten centers from nine countries (Australia, Belgium, Bulgaria, Denmark, Finland, Italy, The Netherlands,

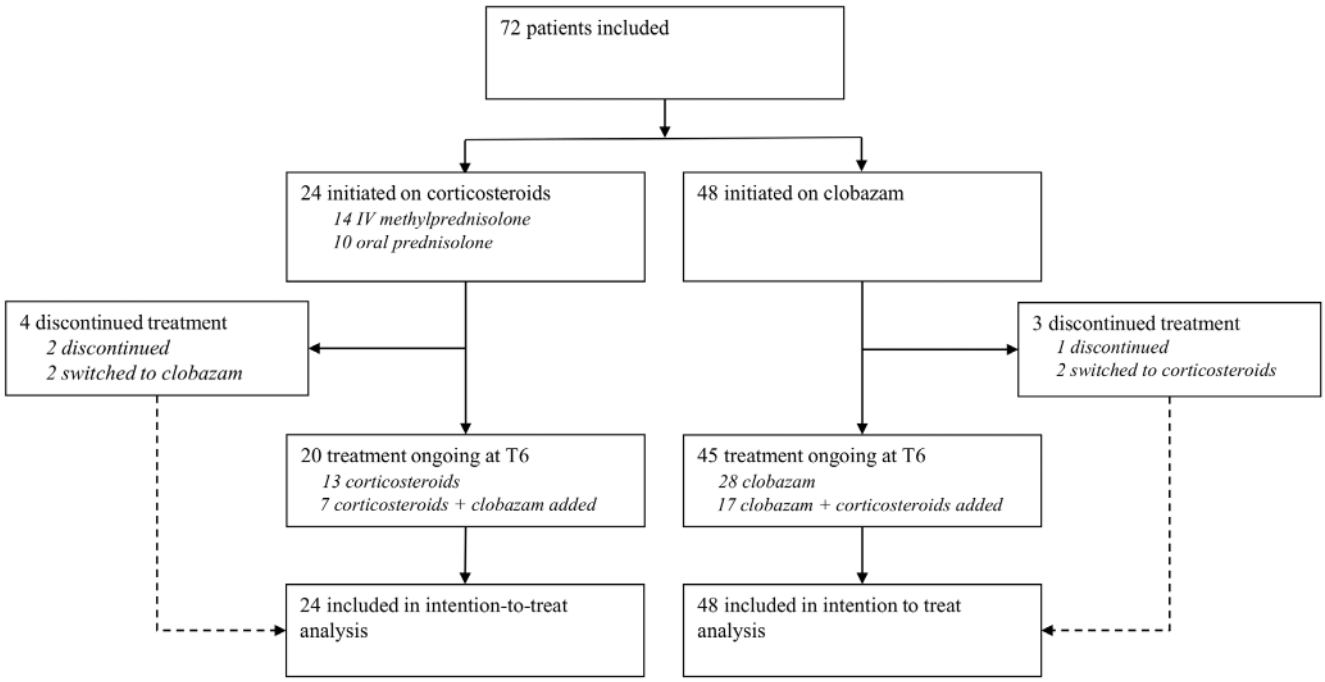

FIGURE 1 Disposition of patients during the 6-month study period.

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Switzerland, and the United Kingdom) took part in the study. Ninety-six patients were assessed for inclusion in the study and 72 met the eligibility criteria. Primary reasons for exclusion were previous treatment with corticosteroid or clobazam, no sufficient baseline data available, or no primary outcome data available after 6 months. Of those enrolled, 48 were started on clobazam (median dose 10.0 mg/day, IQR 7.5–12.5 mg/day) and 24 were started on corticosteroid. Patients treated with oral prednisolone ($n = 10$) received a median dose of 50.0 mg/day (IQR 45–50 mg/day), whereas those treated with IV pulse methylprednisolone ($n = 14$) were given 20 mg/kg once daily for three consecutive days at 4-week intervals.

The baseline characteristics of the patients included in the study are displayed in Table 1. The mean age of all patients at the start of treatment with either corticosteroid or clobazam was 6.7 years (SD 2.0). About one-half (46%) had an established structural or genetic etiology of (D)EE-SWAS and 22% had a normal neurodevelopment prior to the diagnosis (EE-SWAS). The mean IQ of the 38 patients who underwent neuropsychological assessment at baseline was 83 (SD 21). There were no differences in baseline characteristics between the two treatment groups.

Forty percent of 48 patients initially treated with clobazam had either switched to corticosteroid ($n = 2$) or added corticosteroid to their treatment ($n = 17$) after a median time of 13.5 weeks (IQR 10–21) since initiation with clobazam. Similarly, among the 24 patients initiated on corticosteroid, 38% had either switched to clobazam ($n = 2$) or added clobazam ($n = 7$), after a median time of 11.0 weeks (IQR 4–17). As a result, 24 patients were treated with a combination of clobazam and corticosteroid by 6 months. Three patients were no longer treated with either of these agents by 6 months (Figure 1).

3.2 | Disease-related outcomes

An improvement in daily functioning after 6 months (primary outcome) was reported in 84% (20/24) of patients initiated on corticosteroid compared to 51% (24/47) of those initiated on clobazam (RR 1.6, CI 1.2–1.8, $p = .012$).

Delta IQ did not differ between treatments, but it could be assessed in only ≤10 patients per group. No patients in either group met criteria of an IQ responder.

With respect to secondary outcomes, SWI improved after 6 months in the corticosteroid group (median delta SWI −10, IQR −26 to −1), but not in the clobazam group (median delta SWI 0, IQR −20 to 7, $p = .0352$). Other secondary outcome measures did not differ between groups (Table 2).

In a subgroup analysis, no differences in outcome measures were identified at 6 months between patients who received IV methylprednisolone pulse therapy ($n = 23$) and oral prednisolone ($n = 17$) at any time during the treatment course of 6 months, although there was a trend for pulse therapy to be more frequently associated with improved daily functioning (Table 3). Two patients were treated with other corticosteroid: one with dexamethasone and one with hydrocortisone. Both were excluded from this comparison, as was the patient who was treated with both pulsed methylprednisolone and oral prednisolone. There were no IQ responders in either group, and delta IQ could not be meaningfully compared because of the low number of patients with available data.

3.3 | Primary outcome predictors

At univariable and multivariable regression analysis, no predictors for improvement in daily functioning were found (Table 4).

3.4 | Adverse events

Sixteen patients (33%) initiated on clobazam versus 8 patients (33%) initiated on corticosteroid had at least one adverse event during the 6-month study period (RR 1.0, 95% CI 0.4 - 1.7, p = 1.00) (Table 5). The most frequent reported adverse event was fatigue in the clobazam group (10%), and fatigue and weight gain (13% each) in the corticosteroid group.

In a subgroup analysis restricted to patients who were treated with corticosteroid anytime during the treatment course of 6 months, 3 (13%) of the 23 patients who were treated with IV pulse methylprednisolone had at least one adverse event compared to 13 (76%) of the 17 patients treated with oral prednisolone (RR 6.0, 95% CI 3.4–7.1, $p < .001$) (Table 6). The patient who was treated with both pulsed methylprednisolone and oral prednisolone and the two patients treated with other types of steroids were not included in this analysis. In the oral prednisolone group, 8 of 17 patients discontinued within 3 months (compared to 4 of 23 in the pulse methylprednisolone group). The primary reason for treatment discontinuation was not always clear in the medical records. However, all patients in the oral prednisolone group experienced adverse effects, which are likely to have contributed to the decision to discontinue treatment.

4 | DISCUSSION

The results of this multicenter retrospective study reinforce previous evidence supporting the superiority of

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TABLE 1 Baseline characteristics.

	All ($n=72$)	Clobazam ($n=48$)	Corticosteroids ($n=24$)	p-value for comparison
Sex				.87
Male	41 (57%)	27 (56%)	14 (58%)	
Age at onset of seizures, years	4.0 (2.2)	3.9 (2.3)	4.2 (2.0)	.60
Age at (D)EE-SWAS diagnosis, years	6.5 (2.0)	6.5 (2.1)	6.6 (1.9)	.95
Age at start of treatment with corticosteroid or clobazam, years	6.7 (2.0)	6.6 (2.1)	6.9 (1.9)	.59
Seizure type at inclusion				.60
Generalized	14 (20%)	10 (21%)	4 (17%)	
Focal	38 (54%)	25 (53%)	13 (54%)	
Both	10 (14%)	5 (11%)	5 (21%)	
No seizures	9 (13%)	7 (15%)	2 (8%)	
Previously treated with ASM				.69
No	10 (14%)	8 (17%)	2 (8%)	
1–2 ASM	43 (60%)	29 (60%)	14 (59%)	
3–4 ASM	14 (19%)	8 (17%)	6 (25%)	
5–6 ASM	5 (7%)	3 (6%)	2 (8%)	
Etiology of (D)EE-SWAS				.32
Unknown	39 (54%)	24 (50%)	15 (63%)	
Established structural or genetic	33 (46%)	24 (50%)	9 (38%)	
MRI abnormalities[a]	31/66 (47%)	22/43 (51%)	9/23 (39%)	.44
Genetic abnormality[b]	7 (10%)	5 (10%)	2 (8%)	1.0
Psychomotor development before (D)EE-SWAS onset				.77
Normal (EE-SWAS)	16 (22%)	12 (25%)	4 (17%)	
Mildly delayed (DEE-SWAS)	27 (38%)	18 (38%)	9 (38%)	
Moderately delayed (DEE-SWAS)	22 (31%)	13 (27%)	9 (38%)	
Severely delayed (DEE-SWAS)	7 (10%)	5 (10%)	2 (8%)	
Sleep spike–wave index at baseline (median (IQR))	80 (73–90)	80 (70–90)	83 (76–87)	.73
Physiological sleep phenomena present at baseline EEG	44/67 (66%)	31/44 (70%)	13/23 (57%)	.25
Total IQ at baseline neuropsychological assessment	83 (21) $n=38$	83 (23) $n=25$	83 (17) $n=13$	.94

Note: Data are *n* (%) or mean (SD) unless otherwise indicated.

Abbreviations: (D)EE-SWAS, developmental and epileptic encephalopathy with spike–wave activation in sleep; ASM, antiseizure medication; EEG, electroencephalography; IQ, intelligence quotient; MRI, magnetic resonance imaging.

[a]Including infarction ($n=3$), thalamic lesion ($n=7$), periventricular leukoencephalopathy ($n=2$), malformation of cortical development ($n=3$), atrophic/gliotic changes ($n=4$), hydrocephalus ($n=2$), corpus callosum agenesis, and other/unspecified ($n=10$).

[b]Including *KCNB1* pathogenic variant ($n=2$), *KMT2A* variant ($n=1$), *GRIN2A* variant ($n=1$), *MECP2* variant ($n=1$), and deletions of 4q13.1 ($n=1$) and 5q21.2q23.1 ($n=1$).

initial treatment with corticosteroid over clobazam to improve daily functioning in patients with (D)EE-SWAS. The difference in outcomes between groups was large, with 84% of patients initiated on corticosteroid showing an improvement in daily functioning, as judged by a principal investigator based on the medical record, compared with 51% of those started on treatment with clobazam. These results complement the findings of RESCUE ESES, which showed that early treatment with corticosteroid, but not clobazam, was associated with an improved IQ score at 6 months in a small proportion of children with (D)EE-SWAS.[12] Although we could not identify differences in IQ

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TABLE 2 Primary and secondary outcomes at the 6-month assessment in the two treatment groups.

	Clobazam ($n=48$)		Corticosteroids ($n=24$)		RR	
	n (%)	Median (IQR)	*n* (%)	Median (IQR)	(95% CI)	*p*-value
Primary outcome						
Improvement in daily functioning	24/47 (51%)	—	20/24 (84%)	—	1.6 (1.2 to 1.8)	**.012**
Secondary outcomes						
IQ responder[a]	0/10 (0%)		0/9 (0%)		NA	NA
Delta IQ	$N=10$	0 (−7 to 6)	$N=9$	0 (−5 to 0)	—	.34
Delta SWI (%)	$N=41$	0 (−20 to 7)	$N=20$	−10 (−26 to −1)	—	**.035**
EEG responder[b]	7/41 (17%)	—	6/20 (30%)	—	1.8 (.6 to 3.5)	.25
Sleep SWI <50%	7/42 (17%)	—	6/21 (29%)	—	1.7 (.6–3.5)	.28
Occurrence of seizures	25/46 (54%)	—	11/23 (48%)	—	.9 (.5 to 1.3)	.61

Abbreviations: IQR, interquartile range; CI, confidence interval; EEG, electroencephalography; IQ, intelligence quotient; RR, relative risk; SWI, spike–wave index.

Note: Bold indicates significance level at *p*-value < .05.

[a]Defined as improvement of ≥11.25 IQ points.

[b]Defined as SWI decline by ≥25% compared to baseline.

TABLE 3 Comparison of outcomes at the 6-month assessment between patients treated with pulse methylprednisolone and those treated with oral prednisolone.

	Intravenous pulse methylprednisolone ($n=23$)		Oral prednisolone ($n=17$)			
	n (%)	Median (IQR)	*n* (%)	Median (IQR)	RR (95% CI)	*p*-value
Primary outcome						
Improvement in daily functioning	18/23 (78%)	—	10/16 (63%)	—	.8 (.4–1.1)	.29
Secondary outcomes						
Delta SWI (%)	$N=17$	−10 (−25 to 0)	$N=15$	−13 (−32 to −1)	—	.61
EEG responder[a]	5/17 (29%)	—	6/15 (40%)	—	1.4 (.5–2.6)	.53
Sleep SWI <50%	4/18 (22%)	—	6/15 (40%)	—	1.8 (.6–3.4)	.27
Occurrence of seizures	13/21 (62%)	—	8/17 (47%)	—	.8 (.3–1.2)	.36

Abbreviations: IQR, interquartile range; CI, confidence interval; EEG, electroencephalography; RR, relative risk; SWI, spike–wave index.

[a]Defined as SWI decline by ≥25% compared to baseline.

outcomes between the two treatments, the value of this observation is limited by the fact that in the present study pre- and post-treatment IQ scores were available for only 19 children.

In RESCUE ESES, no differences in daily functioning were found between the two treatment groups. In both groups. more than 70% of caregivers and parents reported improvement in daily functioning in their child after 6 months, assessed by a visual analogue scale (VAS) score. However, participants and treating physicians were not masked to treatment, which could have led to biased evaluation of the global daily functioning by over-expectation of treatment effects, a well-known bias issue in non-masked trials.[14] An earlier meta-analysis of 575 children with (D)EE-SWAS, however, suggested differences in subjective cognitive outcomes, with subjective improvement in 70% of those treated with corticosteroid and in 45% of those treated with clobazam.[11] Although the previous literature suggested superiority of initial treatment with corticosteroid, 67% of children

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TABLE 4 Possible predictors for improvement in daily functioning.

	Univariable RR (95% CI; *p*-value)	Multivariable RR (95% CI; *p*-value)
Age (D)EE-SWAS diagnosis	1.0 (.8–1.3; .81)	
Age at first seizure	1.1 (.8–1.4; .53)	
Baseline IQ	1.0 (1.0–1.0; .65)	
Baseline SWI	1.0 (.9–1.0; .13)	1.0 (1.0–1.0; .42)
Normal development prior to (D)EE-SWAS	1.5 (.5–3.5; .60)	
Established etiology	.7 (.3–1.8; .48)	
Number of ASM before inclusion	.8 (.5–1.1; .20)	.9 (.8–1.0; .24)
MRI abnormality	.6 (.2–2.6; .31)	

Abbreviations: (D)EE-SWAS, developmental and epileptic encephalopathy with spike–wave activation in sleep; ASM, antiseizure medication; CI, confidence interval; IQ, intelligence quotient; MRI, magnetic resonance imaging; RR, relative risk; SWI, spike wave index.

TABLE 5 Adverse events reported during the study in the two treatment groups.

	Clobazam (*n* = 48)	Corticosteroids (*n* = 24)
Number of adverse events reported	21	12
Patients that reported at least one adverse event	16 (33%)	8 (33%)
Fatigue	5 (10%)	3 (13%)
Myopathy	1 (2%)	—
Behavioral disturbances	3 (6%)	2 (8%)
Weight gain	3 (6%)	3 (13%)
Abdominal pain	—	1 (4%)
Eye pain	—	1 (4%)
Anger/irritable	4 (8%)	1 (4%)
Moon face	1 (2%)	1 (4%)
Hirsutism	1 (2%)	—
Motor problems	2 (4%)	—
Tics	1 (2%)	—
Increased appetite	—	1 (4%)

Note: Data are *n* or *n* (%).

in this study was initially treated with clobazam. We hypothesize that clobazam is still often considered a more convenient first-line treatment option, given that it typically does not require close monitoring or hospital admission. Of note, in addition to corticosteroid and clobazam, there are other treatments that may be considered for patients with (D)EE-SWAS. However, although corticosteroid and clobazam have been reported effective across the entire (D)EE SWAS population, other drugs seem to show efficacy in particular phenotypes or etiologies (for example sulthiame in (D)EE-SWAS patients with the phenotype of atypical focal epilepsy with centrotemporal spikes or memantine in children with DEE due to gain of function variants in the *GRIN2A* gene[15,16]).

After 6 months, median change in SWI compared to baseline was −10 in the corticosteroid group, compared to 0 in the clobazam group, a statistically significant difference. These findings are in line with previous retrospective studies, where higher EEG response rates have been reported with corticosteroid compared to clobazam.[11,17] In RESCUE ESES, median change in SWI compared to baseline was −5 in the corticosteroid group, compared to 0 in the clobazam group, although this difference was not statistically significant. The clinical relevance of the difference in delta SWI is unclear, since earlier studies did not find a consistent relationship between improvement of EEG abnormalities and improvement of cognitive function.[11,12,18] This suggests that treatment choices in children with (D)EE-SWAS should be guided by cognitive response over EEG parameters. Further

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TABLE 6 Comparison of adverse events between patients treated with intravenous pulse methylprednisolone and those treated with oral prednisolone.

	Methylprednisolone ($n=23$)	Oral prednisolone ($n=17$)
Number of adverse events reported	4	21
Patients that reported at least one adverse event	3 (13%)	13 (76%)
Fatigue	1 (4%)	2 (12%)
Myopathy	1 (4%)	—
Behavioral disturbances	1 (4%)	2 (12%)
Weight gain	—	6 (35%)
Abdominal pain	—	1 (6%)
Eye pain	—	1 (6%)
Anger/irritable	1 (4%)	3 (18%)
Moon face	—	2 (12%)
Hirsutism	—	1 (6%)
Motor problems	—	2 (12%)
Increased appetite	—	1 (6%)

Note: Data are *n* or *n* (%).

research is necessary to assess the mechanisms by which corticosteroid therapy influences cognitive outcome, possibly independently of EEG changes.

Although earlier studies reported that an unknown etiology, a normal development before onset of (D)EE-SWAS, or a shorter regression period were associated with a favorable outcome,[10–12,17] no predictors for treatment response were found in univariable and multivariable regression analysis in our study. This might be explained by the many missing data for potential predictors, and the cohort size was relatively small. In addition, previous studies often defined positive outcomes as those associated with either cognitive or EEG improvement, or both, whereas we focused only on predictors of subjective cognitive improvement.

With respect to tolerability findings, the most interesting difference was related to the type of corticosteroid therapy. Although there was a trend for IV pulse methylprednisolone to be associated with higher rates of improvement in daily functioning (18/23, 78%) compared with daily oral prednisolone therapy (10/17, 63%), pulse therapy also appeared to be much better tolerated. Only 13% of patients treated with pulsed methylprednisolone had at least one adverse event, compared to 76% of patients treated with oral prednisolone. Few studies have directly compared the effects of the two treatment regimens. In RESCUE ESES, differences in efficacy and safety between IV pulse therapy and oral therapy could not be assessed meaningfully because of the smaller sample size. The findings in the present study support previous suggestions that IV pulse therapy has fewer side effects than daily oral administration,[19–21] while being similarly effective.

Our study has several limitations. First, the small number of patients with data available from neuropsychological assessments limits the statistical power to detect differences in objective cognitive outcomes (IQ outcomes), making the results difficult to interpret. Second, using a subjective primary outcome measure that is based on interpretation of medical records by the principal investigator at each participating center carries a risk of observer bias. Third, the study design was observational and allocation to treatment groups was not randomized. Although centers generally managed their patients using protocols similar to those applied in RESCUE ESES, dose regimens were not standardized and were decided by individual physicians. It is possible that children with a more severe clinical presentation were preferentially initiated on corticosteroid, which are generally perceived as a more-effective, yet more-invasive treatment. None of the baseline variables, however, differed between the treatment groups, and therefore the effect of this potential confounder is likely limited. In addition, information on clobazam dose expressed in mg/kg/day was not available for all patients, which prevented assessing the relationship between clobazam dose and clinical outcomes. Fourth, although we applied ITT analysis, which is correct as it focuses on final outcomes in relation to the initial treatment choice, it is important to consider that many patients added (or switched to) the other treatment during the study, leading to 35% of patients taking combined clobazam and corticosteroid therapy at 6 months. Fifth, the short follow-up period of 6 months does not permit conclusions about long-term outcomes.

In summary, our findings complement those of earlier observational studies and, consistently with the results of RESCUE ESES, provide further evidence for superiority

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of treatment with corticosteroid over clobazam in the initial management of patients with (D)EE-SWAS. Our data also suggest that IV methylprednisolone pulse therapy is at least as effective as daily oral prednisolone therapy, but it has the advantage of fewer side effects.

AUTHOR CONTRIBUTIONS

Conceptualization: F.E.J., B.vdM., and K.P.J.B. Methodology: F.E.J., B.vdM., K.P.J.B., M.M.L.vA., L.J.V., E.P., and A.A. Investigation: L.J.V., G.Ru., M.S.K., P.D., V.D.G., L.M., G.Ra., A.J., R.C., LL, F.S.S., H.C.T., K.P.J.B., F.E.J., and B.vdM. Data Analysis: M.M.L.vA., L.J.V. and W.M.O. Writing (Original Draft): M.M.L.vA. (Review & Editing): L.J.V., G.Ru., M.S.K., P.D., V.D.G., L.M., G.Ra., A.J., R.C., L.L., A.A., W.M.O., F.S.S., H.C.T., K.P.J.B., F.E.J., and B.vdM. Supervision: F.E.J. and K.P.J.B. Funding Acquisition: F.E.J. and B.vdM.

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CONFLICT OF INTEREST STATEMENT

M.M.L.vA. reports grants from the Dutch Epilepsy Fund (EpilepsieNL), the Wilhelmina Children's Hospital Research Fund (WKZ fund), and the Ming fund. G.Ru. received speaker's fees from Angelini, UCB and consultancy fees for advisory boards from UNEEG and Angelini, outside of the submitted work. P.D. received consultancy/speakers remuneration from UCB, Angelini, PTC, and Jazz Pharmaceuticals, outside of the submitted work. E.P. received speaker's or consultancy fees from Eisai, GRIN Therapeutics, SK Life Science, Sun Pharma, Takeda, UCB Pharma, and Xenon Pharma and royalties from Wiley and Elsevier, outside of the submitted work. V.D.G. has served on scientific advisory boards for Longboard Pharmaceuticals and Dr. Schar Kanso, and has received grants from Jazz Pharmaceuticals. L.M. received speakers' or consultant/advisor fees from Eisai, GW Pharma, Jazz Pharma, Marinus Pharmaceuticals, Novartis, Orion, Takeda, and UCB Pharma, outside of the submitted work and is member of the board of the Finnish Epilepsy Association and Subassociation of Uusima. A.J. has served as consultant/advisor for GW Pharma (now Jazz Pharmaceuticals) and Novartis for which remuneration was made to the department, outside of the submitted work. R.C. received speaker's or consultancy fees from Eisai, UCB Pharma, and Jazz outside of the submitted work. K.P.J.B. reports grants from the Dutch Epilepsy Fund (EpilepsieNL) and the Ming fund during the conduct of the study. F.E.J. reports grants from the Dutch Epilepsy Fund (EpilepsieNL), the Wilhelmina Children's Hospital Research Fund (WKZ fund), and the Ming fund during the conduct of the study; and has served as consultant/advisor for UCB, GW Pharma (now Jazz Pharmaceuticals), Lundbeck/Longboard, and Novartis for which remuneration was

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

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