ORIGINAL RESEARCH ARTICLE

Eslicarbazepine Acetate as Adjunctive Therapy for Primary Generalized Tonic-Clonic Seizures in Adults: A Prospective Observational Study

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Abstract

Background Eslicarbazepine acetate (ESL), a novel sodium channel blocker, is approved for mono and adjunctive treatment of partial epileptic seizures with or without secondary generalization. Its efficacy in primary generalized seizures has not yet been evaluated.

Objective To evaluate the efficacy and safety of ESL in primary generalized tonic-clonic seizures (PGTCS) in an observational study.

Methods The data were collected from a prospective population-based register. Effectiveness was measured as relative reduction in standardized seizure frequency (SSF), responder rate ($\geq$ 50% reduction in SSF), and seizure freedom rate at 6 and 12 months after initiation of ESL. Safety and tolerability were evaluated using patients' diaries.

Results Fifty-six adult patients with PGTCS were treated with ESL as adjunctive therapy. Of these, 30.4% ($n = 17$) had myoclonic seizures in addition to PGTCS. The retention rate after 12 months was 80.4% ($n = 45$). After initiating ESL therapy, reduction in SSF for PGTCS on ESL was 56.0% after 6 months and 56.9% after 12 months ($p < 0.01$), whereas myoclonic seizures did not show any significant improvement in frequency. The responder rate for PGTCS was 64.3% after 6 months and 66.1% after 12 months, and seizure freedom was achieved in 32.1% and 35.7%, respectively. Forty-three patients (73.2%) reported no side effects. Among the reported side effects of ESL therapy, headache (7.1%), dizziness (8.9%), tiredness (7.1%), nausea (5.4%), and hyponatremia (5.4%) were the most prevalent.

Conclusions Our data suggest that ESL may provide additional benefits in the treatment of patients with PGTCS and motivate randomized controlled trials in this indication.

Key Points

Eslicarbazepine acetate may be beneficial in the adjunctive therapy of primary generalized tonic-clonic seizures.

Slow inactivation of voltage-gated sodium channels could provide a new therapeutic option in primary generalized tonic-clonic seizures.

The results we obtained in this observational study should be confirmed in randomized controlled trials.

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1 Introduction

Epilepsy can be divided into focal and generalized epilepsy syndromes [1]. Idiopathic generalized epilepsies encompass childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy only

with generalized tonic-clonic seizures [1]. The task force of the International League Against Epilepsy (ILAE) on Classification of the Epilepsies recommended two equal terms for these four epilepsy syndromes: "genetic generalized epilepsies" and "idiopathic generalized epilepsy" [1]. Here, we use the term idiopathic generalized epilepsy (IGE). In IGE, absences, myoclonic, or primary generalized tonic-clonic seizures may occur in combination or separately [2]. These types of seizure are accompanied by generalized, bilateral synchronous (poly-)spike wave discharges on the electroencephalogram [3].

IGE typically occurs in childhood and adolescence, may subside in adulthood, and often responds better to medical treatment than focal epilepsy [4]. Nevertheless, it is not uncommon for pharmacoresistant generalized epilepsy to develop in adulthood in 15–40% of cases [5, 6].

Unlike focal epilepsies, the choice of medications and surgical procedures for primary generalized epilepsies is very limited. Of all the antiseizure medications (ASMs) that have been shown to be effective in treating patients with focal epilepsy, only phenobarbital, carbamazepine (CBZ), phenytoin (PHT), valproate (VPA), lamotrigine (LTG), levetiracetam (LEV), topiramate (TPM), and perampanel (PER) have been approved in Europe for treating patients with primary generalized tonic-clonic seizures (PGTCS) [7–11]. Certain ASMs, especially sodium channel blockers, may aggravate myoclonic seizures and absence seizures up to a status epilepticus [12–16].

Successful treatment of refractory IGE requires the use of anticonvulsants with new mechanisms of action. Achieving seizure freedom with as few side effects as possible is particularly important for affected patients [17], reflected by improved quality of life [18, 19]. Therefore, data on the efficacy and safety of novel ASMs in patients with refractory IGE is urgently needed. New ASMs are often first investigated in partial seizures with or without secondary generalization because they are more prevalent in adult populations [20]. Unfortunately, not all pharmaceutical companies proceed to evaluate novel ASMs in primary generalized seizures after their approval for partial seizures [21].

Eslicarbazepine acetate (ESL) is approved for mono and adjunctive treatment of partial epileptic seizures with or without secondary generalization [22]. Its approval was issued in the EU in 2009 and in the USA in 2013, and it has been generic since 2021. ESL is a carboxamide and dibenzazepine derivative closely structurally related to CBZ and oxcarbazepine (OXC) [23].

CBZ has already been shown to be effective on PGTCS [24]. ESL has a different mechanism of action to CBZ, affecting the slow rather than the fast inactivation of sodium channels [25]. Interestingly, lacosamide (LCS) shares the same mechanism of action and has been already been proved in the treatment of PGTCS [10].

In placebo-controlled trials, adverse effects occurred in 60–70% of subjects treated with ESL (compared with 46–49% of subjects treated with placebo) [26]. Adverse effects were mild to moderate and occurred mainly in the first few weeks. The most common side effects are dizziness, fatigue, headache, and nausea [26]. Hyponatremia as a side effect of ESL therapy should also be considered and monitored.

The aim of this observational study was to evaluate the effectiveness and safety/tolerability of ESL as adjunctive therapy in patients with PGTCS.

2 Methods

2.1 Study Design and Clinical Evaluation

Data collection on adult patients with PGTCS treated with ESL as adjunctive therapy was performed using the Mainz Epilepsy Registry (MAINZ-EPIREG). MAINZ-EPIREG is a population-based register of patients with epilepsy who are treated in the Mainz Comprehensive Epilepsy and Sleep Medicine Center (reference area of 4 million inhabitants). All clinical diagnoses of PGTCS were confirmed by EEG records and all patients in our study showed EEG findings consistent with generalized epilepsy. Patients with absence epilepsies were not included, as none of them were treated with ESL in our center.

Effectiveness was measured as relative reduction in standardized seizure frequency (SSF, based on the number of seizures per month), responder rate (≥ 50% reduction in SSF), and seizure freedom rate at 6 and 12 months after initiation of ESL. The monthly SSF at baseline was calculated considering 6 months preceding the initiation of ESL. Seizure frequency was recorded in a systematic way before the initiation of ESL and during the whole study period by means of standardized patients' diaries. Safety and tolerability data were documented as side effects reported by patients during the treatment and documented in their seizure diaries. These data were also documented in a systematic way.

All patients underwent blood examinations and sodium plasma levels were documented during the entire duration of the observation. The plasma concentration of ESL and (R)-licarbazepine was obtained in all patients while they were on the stable dosing. The approximate time of plasma concentration quantification was 10–12 h after intake of ESL. Our study was approved by the local ethics committee and all patients signed informed consent for participation in this study.

2.2 Statistics

The statistical analysis was performed using IBM SPSS Statistics Version 23.0 (IBM Corp., Armonk, NY, USA). The data are presented as mean and standard deviation (SD) or median and range depending on normality of data. A t test was used for comparisons of normally distributed variables. If data were not normally distributed, the Mann-Whitney U test (two independent groups), the Kruskal-Wallis test (more than two independent groups), or the Wilcoxon rank test (two dependent groups) was applied. Statistical significance was assumed at a P value of < 0.05. In case of multiple comparisons, we used the Bonferroni correction.

3 Results

In total, 56 patients with PGTCS were treated with ESL as adjunctive therapy during the study period, of whom 33 (58.9%) were female. Patients with PGTCS alone made up the majority of our sample (69.7%). The remaining patients suffered from juvenile myoclonic epilepsy with both PGTCS and myoclonic seizures. The mean age of patients was 34.5 ($\pm$ 9.0 years). The most commonly used dose of ESL was 800 mg/day (400–1600 mg/day). The mean plasma levels of eslicarbazepine and (R)–licarbazepine were 15.6 ± 3.0 μg/mL and 1.0 ± 0.2 μg/mL, correspondingly.

Data on demographics, clinical parameters of epilepsy, and ASMs are presented in Table 1. The mean duration of epilepsy before starting therapy with ESL was 12.4 ($\pm$ 7.9) years. The mean seizure frequency before starting ESL therapy, the number of ASMs discontinued in the past, and the numbers of adjunctive ASMs are shown in Table 1. The most frequently administered other ASMs were LEV, LTG, and VPA (Table 1). The retention rate after 12 months of ESL therapy was 80.4% ($n = 45$).

Considering all seizures, the mean SSF was 2.5 ($\pm$ 4.8) after 6 months and 3.4 ($\pm$ 5.7) after 12 months, both significantly lower compared to the SSF before starting ESL ($p < 0.01$ each). Compared to baseline, the mean SSF of PGTCS was also significantly lower at 0.8 ($\pm$ 1) after 6 months and 0.8 ($\pm$ 1.1) after 12 months ($p < 0.01$ each). The mean SSF of myoclonic seizures did not differ compared to baseline (9.5 ($\pm$ 7.4) at 6 months, $p = 0.27$; 8.8 ($\pm$ 6.5) at 12 months, $p = 0.18$).

Compared to seizure frequency at the time of initiation of ESL, the relative reduction in SSF for PGTCS was 56.0% after 6 months and 56.9% after 12 months ($p < 0.01$). The response rate in PGTCS on ESL was 64.3% after 6 months and 66.1% after 12 months, and seizure freedom was achieved in 32.1% and 35.7%, respectively (Fig. 1). Myoclonic seizures did not show a good response to ESL, with a relative reduction in SSF of 13.2% and 12.9% at

Table 1 Data on demographics and characteristics of patients with idiopathic generalized epilepsy on eslicarbazepine acetate

Clinical parameters	$N = 56$
Age, years	
Mean $\pm$ SD (range)	34.5 $\pm$ 9.0 (20–52)
Gender, n (%)	
Male	23 (41.1)
Female	33 (58.9)
Duration of epilepsy, years	
Mean $\pm$ SD (range)	12.4 $\pm$ 7.9 (1–32)
SSF (monthly) of all seizures before ESL	
Mean $\pm$ SD (range)	4.8 $\pm$ 6.1 (0.25–31)
SSF (monthly) of PGTCS before ESL	
Mean $\pm$ SD (range)	1.8 $\pm$ 1.1 (0.25–5)
SSF (monthly) of myoclonic seizures before ESL	
Mean $\pm$ SD (range)	10.1 ($\pm$6.3)
Continued use of ESL after 12 months, n (%)	45 (80.4)
Number of ASMs discontinued in the past, n (%)	
0	17 (30.4)
1	22 (39.3)
2	11 (19.6)
≥ 3	6 (10.7)
Number of combined adjunctive ASMs, n (%)	
0	0 (0)
1	36 (64.3)
2	14 (25)
≥ 3	6 (10.7)
Most frequent adjunctive ASMs, n (%)	
Levetiracetam	23 (41.1)
Lamotrigine	23 (41.1)
Valproate	18 (32.1)
Topiramate	10 (17.9)
Clobazam	4 (7.4)
Perampanel	4 (7.4)

ASM anti-seizure medication, *ESL* eslicarbazepine acetate, *PGTCS* primary generalized tonic-clonic seizure, *SD* standard deviation, *SSF* standardized seizure frequency

the above-mentioned respective time points. Only 3.5% of patients with myoclonic seizures became free from this type of seizure after 12 months of ESL treatment.

The combination of ESL with LTG or VPA showed the responder rate of PGTCS of 73.9% and 72.2% at 12-month follow-ups, respectively (Fig. 2). The responder rate in case of the combination of ESL with LEV was 51.1%. TPM, CLB, and PER were used as second or third adjunctive ASMs. Because of the lower number of patients treated with adjunctive TPM, CLB, and PER, statistical analysis was not performed for these subgroups.

Side effects during ESL therapy are shown in Table 2. Hyponatremia up to a minimum of 122 mmol/L was

Fig. 1 Freedom of seizures, responder rate, and seizure reduction 6 and 12 months after initiation of eslicarbazepine acetate. *Statistically significant difference of $p < 0.05$ in group comparison between all seizures and PGTCS with myoclonic seizures at 6 and 12 months, respectively. *PGTCS* primary generalized tonic-clonic seizure, *SSF* standardized seizure frequency
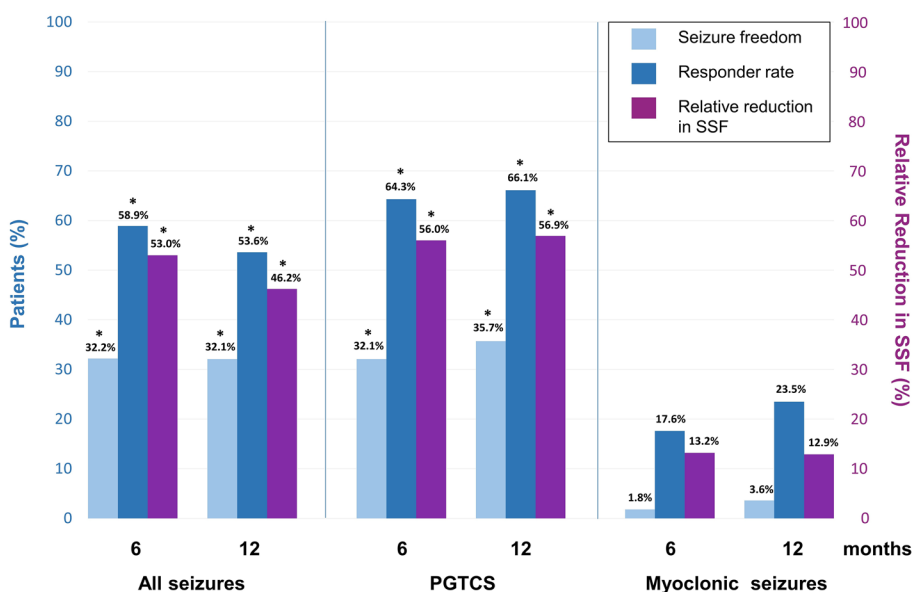

Fig. 2 Responder rate in primary generalized tonic-clonic seizures by adjunctive medication 6 and 12 months after initiation of eslicarbazepine acetate. **Statistically significant difference at $p < 0.01$ in the responder rate of PGTCS in comparison with LEV. [1]Responder defined as a patient with a reduction in seizure frequency of $\geq 50\%$ compared to baseline. *LEV* levetiracetam, *LTG* lamotrigine, *VPA* valproate
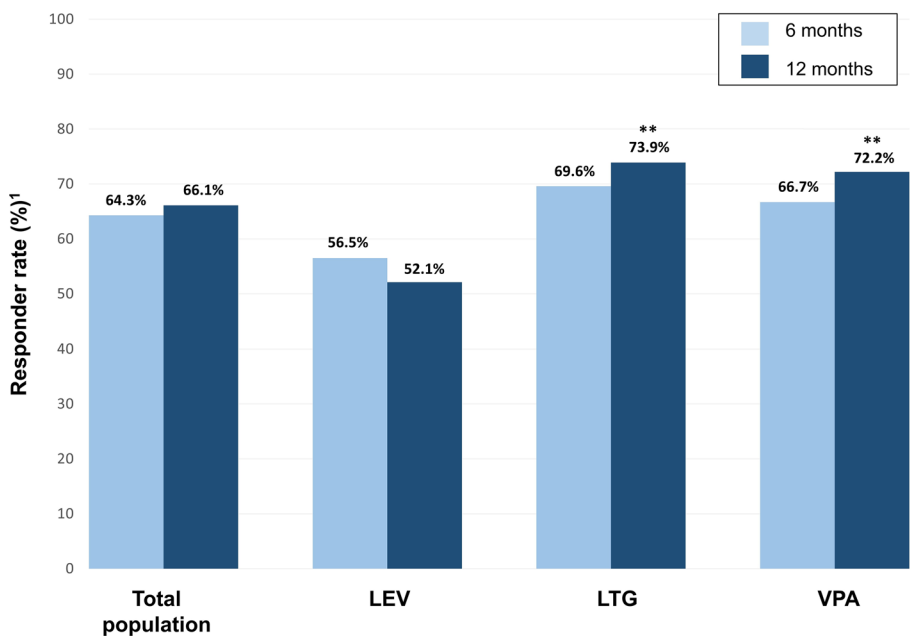
observed in three patients (5.4%). In total 43 patients (73.2%) reported no side effects (Table 2). Thirteen of 19 reported adverse events (68.4%) occurred in patients using a co-medication with LTG. Among patients with juvenile myoclonic epilepsy, 23.5% ($n = 4$) had an increase in myoclonic seizures by up to 50% compared to the time before initiation of ESL. Most frequently, side effects were observed in the combination of ESL with LTG.

Table 2 Adverse side effects, reported by $\geq 5\%$ of patients with idiopathic generalized epilepsy on eslicarbazepine acetate

Adverse side effects	Patients, n (%)
No adverse side effects	41 (73.2)
Headache	4 (7.1)
Dizziness	5 (8.9)
Tiredness	4 (7.1)
Nausea	3 (5.4)
Hyponatremia	3 (5.4)

4 Discussion

The data presented here demonstrate that ESL may be a beneficial treatment for patients with PGTCS. This type of seizure showed a better response to ESL compared to myoclonic seizures. A sub-group of patients even suffered an increase of the frequency of myoclonic seizures.

ESL is a third level derivative of CBZ. CBZ and OXC have already shown a positive effect in the treatment of PGTCS and patients with IGE in previous studies [6, 24, 27]. A recently published study by Cerulli Irelli et al. [6] retrospectively investigated the use of selective sodium channel blockers in 56 patients with IGE. The majority of patients received CBZ and OXC, and only one patient received ESL. For all selective sodium channel blockers combined, that study showed similar responder rates for all seizures (53.5%) at 12 months as in the present paper. In addition, a better responder rate (67.9%) was also observed when only PGTCSs were considered. Similar to our data, a few patients (8.9%) reported worsening of seizures and these were patients with juvenile myoclonus epilepsy. To our knowledge, to date, there is no study that has explicitly investigated ESL in patients with PGTCS. However, the similarity of the mechanisms of action of CBZ, OXC, and ESL suggest a possible overlap in therapeutic effect.

The treatment of IGE can be challenging, and 15–40% of cases are refractory to treatment [5, 6]. The side effects of approved ASM are one of the major reasons for their discontinuation [28]. Especially in patients who do not respond to or do not tolerate standard therapy, a new opportunity appears with each newly introduced ASM [28].

In focal epilepsies, extensive studies have been conducted comparing ESL with other commonly used therapeutic agents [29, 30]. ESL is a well-tolerated ASM that has a slightly different mechanism of action compared to its predecessors, CBZ and OXC. ESL enhances the slow inactivation of voltage-dependent sodium channels [31] similar to LCS [32, 33].

LCS has been shown in previous studies to have good efficacy in patients with generalized epilepsy [10, 11]. A worsening of epileptic seizures described for other sodium channel blockers has also not been shown for LCS [11]. In the present study, worsening was observed only in four patients with myoclonic seizures (23.5%) and in one patient with PGTCS (1.8%). The enhancement of slow inactivation of voltage-gated sodium channels, which is a common mechanism of action in both LCS and ESL, is obviously effective and safe in the treatment of PGTCS. Interestingly, this mechanism of action also shows advantages in the treatment of some definite types of focal epilepsy, such as poststroke epilepsy [34].

Another interesting finding of this study was the significantly better effectiveness of ESL in combination with LTG or VPA than in combination with other ASMs. LTG has shown good efficacy in generalized epilepsy, partly acting through mechanisms of action other than sodium channel blockade [35]. Nevertheless, this combination with ESL and LTG in the present study showed not only a better responder rate but also more side effects overall. In 13 of the 19 reported cases (68.4%) with side effects, patients used LTG as adjunctive medication. However, specific side effects such as dizziness did not occur more frequently with additional use of LTG. Overall, the rate of adverse events of 26.8% was rather low in our study.

Our study has several limitations. This study was an observational study and its findings are inferior to the result of randomized controlled studies. The investigators were not blinded to the therapy regime. The data are based on a moderate sample size, limiting the statistical power for the analysis of sub-groups and different dosages of ESL. However, it is challenging to recruit patients with generalized epilepsy who are taking off-label therapy with a newer ASM. In other studies investigating new ASMs, the number of patients was often similar or even smaller [6, 11]. We did not perform a precise analysis of pharmacokinetics according to the hours since the intake of ESL as this was beyond the scope of our clinical study. As this was not a placebo-controlled study, a possible placebo effect in some patients could not be calculated. The Hawthorne effect was taken into account by the fact that the patient care during the study was not different from the routine patient care in our center outside of a study setting. The intrinsic variability in seizure frequency, which can potentially increase and decrease the outcome of the study, was addressed and attenuated by the long-term observaton of 12 months.

5 Conclusions

Based on these data, ESL can be considered potentially beneficial in the adjunctive therapy of PGTCS. The mechanism of action of slow inactivation of voltage-gated sodium channels could provide a new therapeutic option in this type of seizure. Concomitant myoclonic seizures do not show a good response to ESL and have a risk of deterioration. Controlled randomized studies are needed to determine whether the results from this observational study can be reproduced at a higher level of evidence.

Declarations

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