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EXPERT OPINION

Update on treatment of partial onset epilepsy: role of eslicarbazepine

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Markus Rauchenzauner[1,2]
Gerhard Luef[3]

[1]Department of Pediatrics IV, Medical University Innsbruck, Austria; [2]Neuropediatric Department, Schön Klinik Vogtareuth, Vogtareuth, Germany; [3]Department of Neurology, Medical University Innsbruck, Austria

Abstract: Partial epilepsy comprises simple partial seizures, complex partial seizures, and secondarily generalized seizures, and covers more than 60% of patients with epilepsy. Antiepileptic drugs are generally considered to be the major therapeutic intervention for epilepsy but, despite a broad range of commonly used antiepileptic drugs, approximately 30% of adult patients and approximately 25% of children with epilepsy have inadequate seizure control. Eslicarbazepine acetate (ESL) is a novel voltage-gated sodium channel-blocking agent with presumed good safety and efficacy for adjunctive treatment of patients with drug-resistant partial epilepsy. ESL is a prodrug of eslicarbazepine (the active entity responsible for pharmacologic effects), and is rapidly and extensively hydrolyzed during first pass by liver esterases after oral administration. The half-life of eslicarbazepine at steady-state plasma concentrations is 20–24 hours, compatible with once-daily administration. ESL 800 mg and 1200 mg significantly reduces seizure frequency and shows a favorable safety profile in adult patients with drug-resistant partial-onset seizures, as demonstrated in previous Phase II and III trials. In children, ESL showed a clear dose-dependent decrease in seizure frequency with good tolerability. The most commonly reported adverse events associated with ESL are dizziness, somnolence, nausea, diplopia, headache, vomiting, blurred vision, vertigo, and fatigue. In conclusion, these characteristics suggest that ESL might be a valid and well tolerated treatment option for patients with drug-resistant partial-onset epilepsy. The convenience of once-daily dosing and a short, simple titration regimen would be of special interest for children, although conclusive published data are lacking to date. Hence, there is an urgent need to establish the therapeutic value of ESL in this special population in the near future.

Keywords: eslicarbazepine, partial epilepsy, drug-resistant, antiepileptic drugs

Introduction

Partial epilepsy comprises simple partial seizures, complex partial seizures, and secondarily generalized seizures, and covers more than 60% of patients with epilepsy.[1] Antiepileptic drugs (AEDs) are generally considered to be the major therapeutic intervention for epilepsy, and first-line pharmacologic treatment of partial seizures includes levetiracetam, carbamazepine, oxcarbazepine, sodium valproate, phenytoin, and lamotrigine.

Despite a broad range of commonly used AEDs, approximately 30% of adult patients with epilepsy have inadequate seizure control, and approximately 25% of children with epilepsy experience drug resistance or encounter clinically significant adverse effects.[2,3] Although these suboptimal results usually lead to use of a combination of AEDs, a substantial proportion of patients with epilepsy continue to be therapy-resistant

Correspondence: Markus Rauchenzauner
Neuropediatric Department, Schön Klinik Vogtareuth, Krankenhausstrasse 20, 83569 Vogtareuth, Germany
Tel +49 803 8900
Fax +49 8038 90 4473
Email markus_rauchenzauner@hotmail.com

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despite extension of pharmacotherapy. The aforementioned data have led to widely accepted recommendations for pharmacologic therapy regimes in patients with hard-to-handle seizures for whom epilepsy surgery is not indicated. In the case of a nonresponder to the first AED with the highest tolerated dose, the recommended next step would be to titrate upwards with a second AED, while tapering off the first to switch the patient to an equipotent monotherapy.[4] Of note, there is a growing body of evidence that patients initially not responding to AED treatment possibly achieve seizure freedom with implementation of an AED with an alternative mode of action as a substitute for the prior established drug.[5] Finally, previously published data have suggested that in the event of treatment resistance despite two appropriate AED monotherapy regimens, a third monotherapy trial is expected to have very limited success.[6,7] As a consequence, combination therapy is preferred in the management of drug-resistant epilepsy in adults and children nowadays.

One has to bear in mind that the ongoing introduction of diverse new AEDs for adjunctive use in refractory partial epilepsy has considerably increased the number of potential pharmacologic combinations and interactions in a confusing way. Therefore, the attending physician is urged to appraise various factors when selecting adequate adjunctive agents for polytherapy, comprising efficacy, tolerability profile (adverse effects, mode of action, drug interactions, eg, between AEDs and oral contraceptives), and, especially in childhood, ease of administration. Therefore, there is still the need for development of further AEDs to reduce seizure frequency and improve the safety profile in adults and children with epilepsy.[8–10]

Eslicarbazepine acetate (ESL), a voltage-gated sodium channel (VGSC)-blocking agent, is a third-generation, single-enantiomer member of the commonly prescribed first-line dibenz[*b,f*]azepine family of AEDs (including carbamazepine [first generation] and oxcarbazepine [second generation])[11] with presumed good safety and efficacy for adjunctive treatment of patients with partial epilepsy. In the resting state, the affinity of eslicarbazepine for the VGSC is comparable with that of carbamazepine, with suggested higher inhibitory selectivity for rapidly firing neurons over those displaying normal activity.

After oral administration, ESL is immediately and extensively hydrolyzed to the pharmacologically active entity, eslicarbazepine, during first pass, resulting in an effective half-life of 20–24 hours at steady-state plasma concentrations compatible with once-daily administration. Because eslicarbazepine is chemically related to carbamazepine and oxcarbazepine, with differences at the 10,11 position, eslicarbazepine is not susceptible to metabolic autoinduction, and might have a favorable safety profile and a low drug interaction potential.[12–21] Unlike oxcarbazepine, which is metabolized to both (S)-licarbazepine (80%) and (R)-licarbazepine (20%), eslicarbazepine is metabolized solely to (S)-licarbazepine, although it subsequently undergoes a minor chiral inversion (through oxidation to oxcarbazepine) to (R)-licarbazepine.[22] Other than oxcarbazepine, ESL avoids unnecessary production of enantiomers or diastereoisomers of metabolites and their conjugates.[23] After Phase III trials were completed (mainly in Europe and South America), ESL was approved by the European Medicines Agency and is now available in most European countries as adjunct therapy for adult patients with refractory partial seizures.[24] Of note, no study has been conducted in the US so far.

This paper reviews the efficacy and safety profile of ESL in adults and children with partial epilepsy. The authors conducted a Medline literature search for all publications on eslicarbazepine in clinical and experimental trials, in parallel with a search of congress abstracts.

Mechanism of action

To date, the anticonvulsant efficacy of eslicarbazepine has been evaluated in several animal models, and has proven but weak properties against clonic seizures induced by pentylenetetrazol, bicuculline, picrotoxine, and 4-aminopyridine.[15,18,25] Unfortunately, the precise underlying mechanism of action of eslicarbazepine remains obscure. Eslicarbazepine inhibits, similar to carbamazepine and oxcarbazepine, the release of different neurotransmitters/neuromodulators, namely glutamate, gamma-aminobutyric acid (GABA), aspartate, and dopamine in rat striatal slices. Electrophysiologic studies indicate a competitive interaction of eslicarbazepine acetate and eslicarbazepine with site 2 of the inactivated state of a VGSC in vitro, thus preventing its reversion to the active state and repetitive neuronal firing. Furthermore, tonic extension seizures in maximal electroshock tests in rats and mice and limbic seizures in the corneal-kindled mouse and amygdala-kindled rat are known to be blocked. In addition, analgesic activity in the formalin paw test and in the chronic constriction nerve injury pain model of neuropathic pain in mice has been shown.[11,14,18,25,26]

Pharmacokinetics and pharmacodynamics

The pharmacokinetic and pharmacodynamic profile of eslicarbazepine, as well as the mechanisms of action, differ from those of the well known and frequently used VGSC blockers.[16,27] ESL (BIA 2-093, S-(-)-10-acetoxy-10,11-d

ihydro-5H-dibenz/b,f/azepine-5-carboxamide) is a novel AED that shares with carbamazepine and oxcarbazepine the dibenzazepine nucleus bearing the 5-carboxamide substitute, but is structurally different at the 10,11 position. This molecular variation should lead to the reduction of toxic metabolites, enantiomers, or diastereoisomers without losing pharmacologic activity. The absorption of ESL from the gastrointestinal tract is high, and after oral administration, ESL is extensively metabolized to the main metabolite, eslicarbazepine, the S(+) enantiomer of licarbazepine (S-licarbazepine, (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide). R-licarbazepine and oxcarbazepine (formed by nonmicrosomal cytochrome (CYP) P450-mediated metabolism) are minor metabolites, corresponding, respectively, to approximately 5% and 1% of systemic exposure. Of note, the plasma concentrations of eslicarbazepine have been found below the limit of quantification of the assay (10 ng/mL), with approximately 30% of eslicarbazepine bound to plasma proteins. Eslicarbazepine competitively interacts with site 2 of the inactivated VGSC (with similar affinity to that of carbamazepine), but shows a three-fold lower affinity for the resting state of the channel, suggesting higher inhibitory selectivity of eslicarbazepine for rapidly firing neurons. Glucuronidation and renal excretion are the main metabolic pathways for eslicarbazepine. Minor metabolites in urine are R-licarbazepine, oxcarbazepine, and their glucuronyl conjugates, with renal impairment significantly decreasing the clearance of metabolites. The mean renal clearance from plasma reaches 20–30 mL/min, and the postdose amount recovered in urine is approximately 20% and 40% within 12 and 24 hours, respectively. Previous studies in human hepatocytes show no induction of CYP1A2, CYP3A4, or Phase II hepatic enzymes, and this seems not to be affected by mild or moderate liver impairment. Across a dose range of 400–2400 mg/day, the pharmacokinetics of eslicarbazepine are linear and show dose proportionality. In healthy subjects, maximum observed plasma concentrations were attained at 1–4 hours postdose after single-dose administration, and steady-state plasma concentrations were attained at 4–5 days, reflecting a half-life of 20–24 hours.[12,28] According to pharmacokinetic analyses of data from Phase III studies in adults with epilepsy, the clearance of carbamazepine, phenytoin, topiramate, clobazam, gabapentin, phenobarbital, levetiracetam, and sodium valproate seems to be unaffected by ESL Furthermore, there is a growing body of evidence that acetazolamide, clobazam, clonazepam, gabapentin, lamotrigine, phenobarbital, phenytoin, primidone, and sodium valproate do not interfere with metabolism of ESL.[16,24,28–30]

Efficacy of ESL

The placebo-controlled and open-label studies of ESL performed to date are summarized in Table 1. An early Phase II multicenter, double-blind, randomized, placebo-controlled study was conducted in 143 refractory patients aged 18–65 years with at least four partial-onset seizures per month. The study consisted of a 12-week treatment period followed by a one-week tapering off phase. Patients were randomly assigned to one of three treatment groups, ie, ESL once daily (n = 50), ESL twice daily (n = 46), or placebo (n = 47). The daily dose was titrated from 400 mg to 800 mg and to 1200 mg at four-week intervals. The proportion of responders (patients with ≥50% seizure reduction) was the primary endpoint. The intention-to-treat population included all randomized patients with at least one administration of study medication, while the per protocol population included all patients who completed the study. Testing for superiority of ESL versus placebo (with regard to the proportion of responders) was based on the intention-to-treat population, applying the one-sided *t*-test. ESL was found to be efficacious and well tolerated in adults with refractory partial-onset seizures. The percentage of responders versus baseline showed a statistically significant difference between the once-daily and placebo groups (54% versus 28%; 90% confidence interval [CI]: −infinity, −14; $P = 0.008$). The difference between the twice-daily (41%) and placebo groups did not reach statistical significance (90%

Table 1 Responder rates and decrease in seizure frequency for ESL from three placebo-controlled Phase III trials (intent-to-treat population)

Study	ESL dose (mg/day)	Responder rates (%)[1]	Decrease in seizure frequency[2]
Elger et al[24]	400	23.0	26.0
	800	34.0*	36.0*
	1200	43.0**	45.0**
	Placebo	20.0	16.0
Ben-Menachem et al[16]	400	17.0	18.7
	800	40.0**	32.6**
	1200	37.1*	32.8**
	Placebo	13.0	0.8
Gil-Nagel et al[30]	800	34.5	37.9
	1200	37.7*	41.9*
	Placebo	22.6	17.0

Notes: [1]Seizure frequency reduction ≥50%; [2]Median relative reduction in seizure frequency during the maintenance period; *$P < 0.05$ versus placebo; **$P < 0.001$ versus placebo.

Abbreviation: ESL, eslicarbazepine acetate.

CI: −infinity, −1; $P = 0.12$). A significantly higher proportion of responders in weeks 5–8 was found in the once-daily group than in the twice-daily group (58% versus 33%, respectively; $P = 0.022$). At the end of the 12-week treatment, the number of seizure-free patients in the once-daily and twice-daily groups was 24%, which was significantly different from the placebo group. The incidence of adverse effects was similar between the treatment groups, and no serious drug-related adverse effects occurred.[31]

Three Phase III trials have been completed in a total of 1050 patients enrolled at 125 sites in 23 countries (Tables 1 and 2). All three studies used a multicenter, randomized, double-blind, placebo-controlled, parallel-group design, and included patients with at least four simple or complex partial-onset seizures per four weeks despite treatment with one to three AEDs. The primary analysis of efficacy was based on the intention-to-treat population using an analysis of covariance that models seizure frequency as a function of baseline seizure frequency and treatment. Supportive assessments were performed per protocol. Each study consisted of an eight-week baseline period, followed by double-blind two-week titration and a double-blind 12-week maintenance period. There were three ESL dose groups (400 mg, 800 mg, or 1200 mg once daily) in two studies but only two ESL dose groups (800 mg and 1200 mg once daily) in one study. Between 64% and 75% of patients in each of the Phase III studies were using two concomitant AEDs, the most common of which was carbamazepine. One was a double-blind, placebo-controlled, parallel-group, multicenter study consisting of an eight-week baseline period, after which patients were randomized to placebo (n = 87) or once-daily ESL 800 mg (n = 85) or 1200 mg (n = 80). Patients received a half dose during the two weeks preceding a 12-week maintenance period. Seizure frequency over the maintenance period was significantly ($P < 0.05$) lower than for placebo in both ESL groups. The responder rate was 23% (placebo), 35% (ESL 800 mg), and 38% (ESL 1200 mg). Median relative reduction in seizure frequency was 17% (placebo), 38% (ESL 800 mg), and 42% (ESL 1200 mg), as shown in Table 1. The most common adverse effects (>10%) were dizziness, somnolence, headache, and nausea. The majority of adverse effects were of mild or moderate severity. The authors concluded that once-daily treatment with ESL 800 mg and 1200 mg was effective and generally well tolerated.[30]

Table 2 Summary of adverse events from three placebo-controlled Phase III trials

Adverse events	Percentage of patients	
	All doses of ESL (n = 760)	Placebo (n = 289)
Any adverse event		
Dizziness	22.2	7.4
Somnolence	13.2	9.4
Headache	11.0	8.8
Nausea	10.3	1.3
Vomiting	7.9	3.2
Diplopia	7.3	1.7
Serious adverse events		
Deaths	0.0	0.3

Abbreviations: n, number of patients; ESL, eslicarbazepine acetate.

The other multicenter, parallel-group study consisted of an eight-week, single-blind, placebo baseline phase, after which patients were randomized to placebo (n = 102) or once-daily ESL 400 mg (n = 100), 800 mg (n = 98), or 1200 mg (n = 102) in the double-blind treatment phase. The ESL starting dose was 400 mg. Thereafter, ESL was titrated in weekly 400 mg steps to the full maintenance dose (12 weeks). ESL 400 mg, 800 mg, and 1200 mg once daily was well tolerated and more effective than placebo in patients who were refractory to treatment with one or two concomitant AEDs (Table 1).[24]

Another double-blind, parallel-group, multicenter study consisted of an eight-week observational baseline period, after which patients were randomized to placebo (n = 100) or once-daily ESL 400 mg (n = 96), 800 mg (n = 101), or 1200 mg (n = 98). Patients then entered a 14-week, double-blind treatment phase. All patients started on their full maintenance dose except for those in the ESL 1200 mg group who received once-daily ESL 800 mg for two weeks before reaching their full maintenance dose. Four-week seizure frequency (the primary endpoint) over the 14-week, double-blind treatment period was significantly lower than for placebo in the ESL 800 mg and 1200 mg groups (each $P \leq 0.001$). Responder rate (≥50% reduction in seizure frequency) was 13.0% (placebo), 16.7% (ESL 400 mg), 40.0% (ESL 800 mg, $P \leq 0.001$), and 37.1% (ESL 1200 mg, $P \leq 0.001$). Median relative reduction in seizure frequency was 0.8% (placebo), 18.7% (ESL 400 mg), 32.6% (ESL 800 mg, $P \leq 0.001$ versus ESL 400 mg and placebo), and 32.8% (ESL 1200 mg, $P \leq 0.001$ versus ESL 400 mg and placebo, Table 1). Discontinuation rates due to adverse effects were 3.0% (placebo), 12.5% (ESL 400 mg), 18.8% (ESL 800 mg), and 26.5% (ESL 1200 mg). The most common (>5%) adverse effects in any group were dizziness, somnolence, headache, nausea, diplopia, abnormal coordination, vomiting, blurred vision, and fatigue. The majority of adverse effects were of mild or moderate severity. Treatment with once-daily ESL 800 mg and 1200 mg was more effective

than placebo (Table 1) and generally well tolerated in patients with partial-onset seizures refractory to treatment with one to three concomitant AEDs.[16]

To evaluate the long-term efficacy and safety of once-daily ESL as adjunctive therapy for partial-onset seizures in adults with epilepsy, a one-year, open-label treatment extension with ESL in patients who completed a placebo-controlled pivotal study was conducted. The starting dose was 800 mg once daily for four weeks and, thereafter, the dose could be titrated up or down, and doses of concomitant AEDs had to be kept stable. Overall, 314 patients were enrolled. The intent-to-treat population consisted of 312 patients, of whom 239 (76.6%) completed one year of treatment. The median ESL dose was 800 mg once daily. Compared with baseline, median seizure frequency decreased by 39% during the first four weeks, and by 48%–56% thereafter. The responder rate was 41% during weeks 1–4 and ranged between 48% and 53% thereafter. The proportion of seizure-free patients per 12-week interval ranged between 8.7% and 12.5%. Quality of life, as measured by the Quality of Life in Epilepsy Inventory-31, and depressive symptoms, as measured by the Montgomery Asberg Depression Rating Scale, improved significantly compared with baseline. Adverse effects were reported by 51% of patients. The most frequent adverse effects were headache (10%), dizziness (10%), diplopia (5%), and nasopharyngitis (5%). Adverse effects were mostly (97%) of mild to moderate intensity. Eleven patients (3.5%) discontinued therapy due to adverse effects, and there were no results of laboratory tests raising safety concerns. Sustained therapeutic effect, favorable tolerability and safety, and an improvement in quality of life and depressive symptoms were observed during long-term add-on treatment with once-daily ESL in adults with partial-onset seizures.[32]

Recently, the results of two single-blind studies conducted to evaluate the cognitive and psychomotor effects of ESL and oxcarbazepine following single and repeated administration in healthy volunteers have been reported. The cognitive and psychomotor evaluation consisted of several computerized and paper-and-pencil measures. ESL and oxcarbazepine had similar overall cognitive profiles and did not cause clinically relevant cognitive impairment. The incidence of adverse events was lower with ESL than with oxcarbazepine.[33]

Studies in children

Especially in children, there is a need for new, safe, and effective AEDs to extend the therapeutic armamentarium, particularly in drug-resistant epilepsy. There is increasing literature supporting the fact that about 25% of children with epilepsy experience pharmacoresistance or have to face significant side effects with AED treatment, representing a huge burden to young patients and their families.[2,6] Because ESL 800 mg and 1200 mg once daily significantly reduced the frequency of partial-onset seizures and showed a favorable safety profile when administered as adjunctive therapy in adults, a relatively low-dose tablet formulation (200 mg) and an oral suspension formulation (50 mg/mL) were developed (bioequivalent to the adult tablet formulations).[19] To date, only one Phase IIa clinical trial has explored the pharmacokinetics, efficacy, and tolerability of ESL in children.[29] In order to study three different dosage regimes in each age group (Group 1: 2–6 years, Group 2: 7–11 years, and Group 3: 12–17 years), the following titration design was used: 5 mg/kg/day (weeks 1–4), 15 mg/kg/day (weeks 5–8), and 30 mg/kg/day or 1800 mg/day (weeks 9–12). Similar to what has been described in adults elsewhere, ESL showed extensive first-pass biotransformation to ESL. Accordingly, R-licarbazepine and oxcarbazepine were minor metabolites, corresponding to 4%–7% and 1%–2% of systemic exposure to ESL (comparable with adults). The main metabolic pathway for ESL is glucuronidation, and renal excretion comprises two-thirds in the unchanged form and one-third as a conjugate with glucuronic acid. As a consequence, ESL clearance (and clearance of other metabolites) is affected by renal function, whereas glucuronidation and/or formation of R-licarbazepine or oxcarbazepine seem to be unaffected by liver impairment.[34] As seen in previous studies of other AEDs, clearance in children is higher than in adults. This is backed up by a study done by Almeida et al showing an age-dependent area under the plasma concentration-time curve in the dosing interval (AUC_{0-24}) due to faster plasma clearance of eslicarbazepine in the younger age groups.[29,35] With respect to efficacy, the above-mentioned study also showed a clear dose-dependent decrease in seizure frequency with good tolerability. The median relative change in seizure frequency (when compared with baseline) was −28.2%, −24.8%, and −40.6% in Group 1 (5 mg/kg/day, 15 mg/kg/day, and 30 mg/kg/day, respectively), −11.7%, 5.0%, and 12.2% in Group 2, and −17.1%, −31.7%, and −43.1% in Group 3. However, with the maximum dosage of 30 mg/kg/day, adverse effects were mainly related to the nervous system and tended to be more frequent and more severe. From a pediatrician's point of view, the lack of an influence of ESL on the clearance of sodium valproate, topiramate, phenobarbital, carbamazepine, clobazam, gabapentin, and levetiracetam, as well as no evidence of QT prolongation, is of importance (although the evaluation of electrocardiogram recordings during clinical trials showed an increase in PR interval in

ESL-treated adults, which was highest in the 1200 mg dose group when compared with placebo).[29]

Drug interactions

In vitro studies

Several in vitro studies did not reveal a major influence of warfarin, diazepam, digoxin, phenytoin, and tolbutamide on ESL plasma protein binding. As mentioned earlier, studies with ESL showed no significant induction of CYP1A1, CYP3A, and Phase II enzymes (involved in the glucuronidation and sulfation of 7-hydroxy-coumarin) in fresh human hepatocytes. The activity of CYP1A2, CYP2A6, CYP2B6, CYP2D6, CYP2E1, CYP3A4, and CYP2C9 was not affected, and only a moderate inhibitory effect on CYP2C19 (by 38%), as well as a moderate increment of UDP-glucuronosyltransferase 1A1-mediated ethinylestradiol glucuronidation (by 39%), was seen in the presence of ESL in human liver microsomes in vitro.[36]

In vivo studies

To date, two studies have investigated possible interactions within the field of anticonvulsants. First, a multiple-dose, open-dose, open-label, one-sequence study in two parallel groups of 16 healthy male volunteers with ESL 1200 mg once daily and topiramate 200 mg once daily was conducted.[37] Second, ESL and lamotrigine plasma concentrations and AUC_{0-24} were calculated in an open-label study in two parallel groups of 16 healthy subjects.[28] The authors of both studies did not report any significant pharmacokinetic interactions and, as a consequence, no dose adjustment seems to be required when combining these drugs.[28,37] The prevalence of epilepsy is similar between the genders, and gender-related differences in drug response are due to various factors (including percentage of body fat and fat free mass, body weight, and glomerular filtration rate).[38] In a study by Falcao et al in 12 healthy female and 12 healthy male subjects, gender-related differences in systemic exposure to ESL were marginal and statistically not significant. Therefore, the authors concluded that dose adjustments of ESL based on gender will not be required.[39] Finally, studies concerning possible influences of warfarin (at a subtherapeutic level)[40] or food[41] on ESL pharmacokinetics in healthy volunteers revealed no influence of either on ESL pharmacokinetics, but did show a small and statistically significant reduction in systemic exposure to S-warfarin, with no effect on R-warfarin, on the International Normalized Ratio.[40,41]

Safety and tolerability

With regard to the safety and tolerability of ESL in patients with epilepsy, adverse effects occurred mainly during the early treatment phase; intensity was mild to moderate, and no significant differences in the incidence of adverse effects were apparent between ESL and placebo after six weeks of treatment (Table 2).[16,24,29,30] Of note, the incidence of rash was 0.3% with placebo, 0.5% with ESL 400 mg, 1.1% with ESL 800 mg, and 3.2% with ESL 1200 mg. Furthermore, hyponatremia (<125 mmol/L) was reported in four patients, and the incidence of behavioral or psychiatric adverse events was <1%. Because adverse effects in patients treated with ESL 800 mg seem to be less likely related to the study medication and, as a consequence, less likely to lead to discontinuation, a dosage of 800 mg appears to show the best benefit to risk ratio. Finally, and to summarize the Phase III studies, the overall incidence of adverse effects leading to discontinuation of therapy was low (4.5% with placebo, 8.7% with ESL 400 mg, 11.6% with ESL 800 mg, and 19.3% with ESL 1200 mg). When pooling all adults with epilepsy included in the placebo-controlled studies, 45.3% treated with ESL versus 24.4% treated with placebo reported possible treatment-related adverse effects. As shown in Table 2, the observed frequency of possibly related adverse effects with an incidence >2% were dizziness (18.8% versus 5.7%), somnolence (11.2% versus 8.4%), nausea (6.5% versus 2.4%), diplopia (6.3% versus 1.2%), headache (5.5% versus 2.1%), vomiting (4.8% versus 1.2%), abnormal coordination (4.4% versus 1.8%), blurred vision (3.5% versus 0.9%), vertigo (2.1% versus 0%), and fatigue (2.1% versus 1.8%).[16,18,24,29,30]

In conventional preclinical studies concerning toxicology, genotoxicity, reproductive toxicity, and carcinogenicity, no findings of special concern for human use have been described to date.[18]

Conclusion

The overwhelming majority of adults and children suffering from monotherapy-resistant partial epilepsy have to be treated with adjunctive agents as add-on therapy. However, guidelines for AED combination therapy are sparse and often empiric, especially in children. Rational polypharmacy has to include efficacy, safety and tolerability, toxicology, modes of action, and potential drug interactions. The convenience of once-daily dosing and a short/simple titration regimen, in combination with a favorable efficacy and safety profile, might promote ESL as a valid alternative to the current adjunctive AED therapy armamentarium for drug-resistant partial seizures.

The results of previous Phase II and III studies have demonstrated and confirmed the efficacy and tolerability of ESL 800 mg and 1200 mg once daily as add-on therapy for patients with drug-resistant partial-onset seizures.[16,24,30,31] Interestingly, in patients treated with carbamazepine or lamotrigine, no differences in ESL efficacy were observed when compared with patients not treated with concomitant VGSC blockers. Because there is some evidence of improved efficacy when combining different VGSC blockers, it seems reasonable to evaluate the effect of ESL given together with carbamazepine or lamotrigine.[42] The precise mechanisms underlying the potential efficacy of ESL as adjunctive therapy in patients refractory to other VGSC blockers remain unclear and seem to be multifactorial (eg, different mechanisms of action, pharmacokinetics, and pharmacodynamics for ESL).[28] Hypothetically, patients with drug-resistant epilepsy might have altered VGSC protein subunits, leading to diminished response to diverse AEDs.[43] Furthermore, different neuron types may be more or less prone to seizure-induced changes in transcriptional plasticity, changing susceptibility of some channel proteins to AED treatment.

From a clinical point of view, the incidence of adverse effects and possibly adverse effects associated with ESL treatment is of outstanding importance, especially in children and adolescents. The overall incidence of adverse effects and possibly treatment-related adverse effects seems to increase with increasing dose, and patients are more susceptible during the early phase of treatment. Importantly, and as stated by different authors in previous studies, no changes in laboratory parameters possibly indicating a safety concern regarding the risk for hyponatremia or dyslipidemia, as well as changes in body weight, were seen. ESL may not cause QT prolongation, but the evaluation of electrocardiogram recordings during clinical trials showed an increase in PR interval in ESL-treated patients, which was highest in the 1200 mg dose group compared with the placebo group. Finally, ESL was associated with very few psychiatric events, and the incidence of rash was low.[12,14,16–18,24,29–31,35,40,44,45]

It is well known that a fixed portion of epilepsies start in childhood, so it is of prime importance to broaden possible valuable and safe alternatives to well established AEDs for the treatment of drug-resistant partial epileptic seizures in this age group. Previous findings suggest a potential antiepileptogenic effect of ESL in children and adolescents.[29] Dose regimes of 5–15 mg/kg/day are well tolerated, whereas treatment with a higher dosage (30 mg/kg/day) leads to more frequent and more severe reporting of adverse effects.[29] Clinical efficacy and safety trials on ESL are ongoing in children and adolescents, and the data already published are far from conclusive, so the therapeutic value of ESL in this special population has yet to be established.

Disclosure

The authors report no conflicts of interest in this work.

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