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Efficacy and safety of eslicarbazepine acetate monotherapy for partial-onset seizures: Experience from a multicenter, observational study

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ABSTRACT

Eslicarbazepine acetate (ESL, Aptiom™) is a once-daily anticonvulsant, approved as adjunctive treatment of partial-onset seizures (POS). Historical-controlled trials investigating the use of ESL as monotherapy have demonstrated a favorable efficacy and tolerability profile in patients with POS. This prospective, non-interventional study recruited POS patients in 17 hospitals in Spain. After a 3-month baseline period, ESL therapy was initiated as 400 mg QD and up-titrated to an optimal maintenance dose based on clinical response and tolerance. The incidence of seizures was assessed via seizure calendars and the nature and severity of adverse events (AEs) were also recorded. A total of 117 patients (aged 9–87 years) enrolled in the study and were treated with ESL at either 400 mg/day (3.4% patients), 800 mg/day (61% patients), 1200 mg/day (27.1% patients) or 1600 mg/day (8.5% patients). At 3 months, 82.0% (n = 72) of patients achieved a ≥50% reduction in seizure frequency, compared to 79.7% (n = 67) of patients at 6 months and 83.0% (n = 49) at 12 months. Patients who suffered secondary generalized tonic-clonic (SGTC) seizures had seizure-free rates of 71% (n = 27), 69.6% (n = 29), and 72.7% (n = 16) at 3, 6, and 12 months, respectively. Overall, 18 patients (15.3%) reported AEs of instability and dizziness (n = 9), somnolence (n = 3), mild hyponatremia (n = 3), headache (n = 1), hypertriglyceridemia (n = 1), and allergic reaction (n = 1), which caused ESL discontinuation of ESL treatment. ESL is effective and well tolerated as monotherapy for patients with POS, which supports previous findings. Early use is supported by its frequent use as monotherapy in this study and lack of severe side effects.

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1. Introduction

Eslicarbazepine acetate (ESL) is a once-daily (QD) antiepileptic drug (AED) that was approved by the European Medicines Agency (EMA) [Zebinix™] in 2009 and the US Food and Drug Administration (FDA) [Aptiom™] in 2013 as adjunctive therapy in adults with refractory partial-onset seizures (POS), with or without secondary generalization [1,2]. ESL belongs to the dibenzazepine carboxamide class of AEDs, which also includes carbamazepine (CBZ) and oxcarbazepine (OXC), but differs from CBZ and OXC in its molecular structure, resulting in differences in metabolism and pharmacology [3].

The efficacy and safety of ESL at doses of 800 to 1200 mg per day as adjunctive therapy in adults with POS have been established in double-blind, placebo-controlled studies [4–6]. Additionally, 1-year open-label extension studies demonstrated long-term safety and maintenance of therapeutic effect with ESL [7,8]. More recently, studies investigating the use of ESL as monotherapy have shown favorable results, leading to its approval in monotherapy in USA, but not in Europe [9,10]. These two clinical trials (Study 093-045 and Study 093-046) evaluated the efficacy of ESL (1200 or 1600 mg once daily) by comparison with a historical control group using individual patient data from eight previously completed withdrawal to monotherapy studies [9,10]. Study retention rates for ESL 1600 and 1200 mg QD were superior to the historical control for both studies, suggesting that ESL would be effective as monotherapy in patients with POS [9,10].

The aim of the present study was to gather real-life data on retention and modalities of ESL use when administered as monotherapy in patients with POS.

2. Methods

2.1. Study design

This was a prospective, non-interventional study of POS patients (simple partial, complex partial, and secondary generalized) conducted under conditions of normal clinical practice in 17 hospitals in Spain from January 2011 to December 2014. The study began with a 3-month baseline period prior to transition to ESL monotherapy. During this period, a daily diary was used to record the date, time, type and duration of seizures. Baseline demographics, physical examination, weight, vital signs, medical history, including history of patient's seizures, seizure type and epilepsy syndrome, seizure frequency, prior treatment, and AED prescription were also recorded.

Patients were transitioned to ESL monotherapy in three ways:

1. Initial monotherapy (IM): ESL-naïve patients not currently taking any other AEDs were started on ESL monotherapy.
2. Switch therapy (ST): patients previously taking OXC or CBZ were switched to ESL monotherapy.
3. Conversion to monotherapy (CM): patients taking one or more AEDs, including ESL, were converted to ESL monotherapy by progressive reduction of background AEDs.

Available data corresponding to certain specific and clinically relevant parameters were captured at regular timepoints (3 months, 6 months, and 12 months).

Written informed consent was obtained from all patients, and each patient's eligibility was assessed prior to the enrollment. Seizure types were classified according to the International League Against Epilepsy (ILAE). The study was designed and conducted in accordance with all relevant regulations and guidelines. The study protocol was approved by the Ethics Committee of Hospital Ruber Internacional in Madrid, Spain.

2.2. Patients

Patients were eligible for inclusion if they met the following criteria: male or female patients with partial epilepsy, as defined by the International League Against Epilepsy [11], in whom ESL was considered to be the best choice of treatment by the treating clinician based on patient profile and epilepsy clinical characteristics. Although no age limit was established in this observational study design, the age range was 9 to 87 years.

2.3. Treatment

Patients were treated with ESL according to the approved package insert [1] and as per the discretion of the physician. ESL therapy was initiated as 400 mg once-daily. The dose was up-titrated to an optimal maintenance dose based on clinical response and tolerance. Dose titration was adjusted by each clinician according to seizure frequency and severity, and patient tolerability.

2.4. Efficacy assessments

Efficacy was assessed by comparing reduction in mean seizure frequency and seizure-free rates during a three-month baseline period prior transition to ESL monotherapy with the response at 3, 6, and 12 months' post initiation of ESL monotherapy. Seizure freedom was defined as complete seizure control on ESL monotherapy during the evaluated study period. Seizure frequency was assessed in each clinic visit by reviewing seizure calendars and direct questioning to patients and witnesses. Statistical analyses were performed with R 3.1.2 software [12]. Descriptive statistics were selected according to the characteristics of the variables. Association analyses between clinical and demographic variables and seizure freedom at 3, 6, and 12 months were performed with the Fisher's exact test for categorical variables, and the Wilcoxon rank sum test for quantitative variables. Paired Wilcoxon ranked sum tests were applied to compare the mean seizure frequency at baseline and after 3, 6, and 12 months of ESL therapy.

2.5. Safety assessments

All AEs (both patient- and investigator-reported) were recorded during the study period based on patient reports and physical examination during each visit or by phone between each visit. The nature and severity of the AEs were also recorded. Descriptive statistics were used for data analysis.

3. Results

3.1. Patient demographics and baseline characteristics

A total of 117 patients from 17 hospitals were enrolled in the study, of whom 66 (56.4%) were men (Table 1). The mean age was 42.9 years (range 9–87, SD 16.9). The average disease duration (time between diagnosis and enrollment) was 14.1 years (range 1–54, SD 13.6). The etiology of epilepsy was cryptogenic in 67 (57.2%) patients, symptomatic in 49 (41.8%) patients, and idiopathic in one (0.8%) patient. During the 3-month baseline period, a total of 95 (81.2%) patients had experienced seizures during the 3 months prior to ESL initiation, while 22 (18.8%) patients had experienced no seizures during this period. Overall, the average number of seizures during the 3 months prior to ESL initiation was 3.66 (range 0–12). Secondary generalized tonic-clonic (SGTC) seizures were the most common type of seizure, accounting for 50 (42.7%) patients, followed by complex partial seizures in 40 (34.1%), and simple partial seizures in 27 (23.2%). In this cohort, up to 61.5% of patients had suffered SGTC seizures at some point in their medical history.

Eslicarbazepine acetate was prescribed as initial monotherapy in 31 (26.5%) patients, while monotherapy was achieved after switching from another AED in 18 (15.3%) and as conversion to monotherapy in 68 (58.1%) patients. Reasons for treatment delay in the subgroup of patients taking ESL monotherapy from the beginning were initial