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Two-year follow-up with eslicarbazepine acetate: a consecutive, retrospective, observational study

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KEYWORDS
Eslicarbazepine acetate;
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Summary
Purpose: Eslicarbazepine acetate (ESL) is a new generation voltage-gated sodium channel blocker. It has completed one phase II clinical trial and three phase III clinical trials, two of which with 1-year open label extensions.

ESL was approved in 2009 by the European Medicines Agency as adjunctive therapy in adults with partial-onset seizures with or without secondary generalization. It is marketed in Portugal since April 1st 2010.

Despite good safety and efficacy shown in clinical trials, little is known about its effectiveness in a clinical day-to-day setting.

Our purpose was to assess the post-marketing experience with ESL in our centre, in terms of safety and efficacy profile, and ascertain whether the results were comparable to the published data.

Methods: This is a retrospective, consecutive, single-centre 2-year observational study. All the patients who initiated treatment with ESL between April 1st 2010 and October 31st 2011 at Hospital de Santo António were consecutively included. Data was collected on demographics, clinical features, adverse events and treatment response, using a standardized data form. Follow-up data was considered until October 31st 2013. Efficacy analysis was performed using an ''intention to treat'' approach.

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Key findings: We included 152 patients, 74 (48.7%) female. Mean age was 38.5 years-old (sd = 14.2). Eight patients were less than 18 years old. Mean epilepsy duration was 26.8 (sd = 13.1) years and mean seizure frequency in the previous 3 months was 19.7 seizures per month. At baseline, about 57.9% of all patients were taking ≤2 concomitant AEDs.
The total adverse rate was 42.1% (64/152), with 50.0% (32/64) leading to treatment discontinuation. The most frequent adverse events were dizziness and somnolence/slowness. Adverse events were higher in regimens including carbamazepine, and mean age was higher in the patients reporting adverse events.
Retention rates as estimated by Kaplan—Meyer curves were 82.9%, 71.3%, 65.1% and 62.8%, respectively, at 6, 12, 18 and 24 months. Retention time was not influenced by gender, diagnosis, age or epilepsy duration. Fifty-six patients (36.8%) dropped out of treatment, 32 (57.1%) due to adverse events, 19 (33.9%) due to lack of efficacy and 5 (8.9%) for other reasons.
At 6,12,18 and 24 months, the responder rates were 25.7%, 25.7%, 19.0% and 17.1%, respectively and favourable global clinical impression rates were 27.7%, 19.7%, 17.8% and 16.5%.
Significance: This is the first study reporting follow-up data for up to 2 years in patients treated with ESL in the setting of daily clinical practice.
The retention rates in our study are sustained throughout the 2 years of follow-up, and at 6 and 12 months are globally comparable to those of phase III trials and open-label extensions. The adverse event rate is also comparable to previous studies, and no new safety issues attributable to ESL were found.
Responder rates were lower than those of previous studies, even though efficacy results must be interpreted with caution given the different study design.
Thus, ESL appears to be a clinically useful add-on AED, with good safety profile and high retention rates, even in a very refractory group of patients like the presented cohort.

Introduction

Eslicarbazepine acetate (ESL) is a new generation voltage-gated sodium channel blocker (Almeida and Soares-da-Silva, 2007). ESL is chemically related with carbamazepine and oxcarbazepine, as all three share the dibenzazepine nucleus, but is structurally different at the 10,11-position (Benes et al., 1999). This molecular distinction results in differences in metabolism (Hainzl et al., 2001). It is extensively metabolized to S-licarbazepine (Falcao et al., 2007; Perucca et al., 2011), which is believed to be responsible for the antiseizure effects (Pekcec et al., 2011; Pires et al., 2011; Sierra-Paredes et al., 2011; Soerensen et al., 2011; Torrao et al., 2011). Blockade of voltage-gated sodium channels, but also of type T calcium channels, are believed to be the main mechanisms of action (Hebeisen et al., 2011; Brady et al., 2011). Phase I studies showed that peak plasma concentration was obtained at 1—4 h after dosing and that steady-state plasma levels were attained after 4—5 days, consistent with an effective half-life of 20—24 h (Almeida and Soares-da-Silva, 2003, 2004; Almeida et al., 2005). Subsequently, the phase II clinical trial showed that ESL can be administered as a once-daily dosing (Elger et al., 2007).

It has completed one phase II clinical trial and three phase III clinical trials: BIA 2093—301 (Elger et al., 2009), BIA 2093-302 (Ben-Menachem et al., 2010), BIA 2093-303 (Gil-Nagel et al., 2009). The three phase III studies had similar designs in which following a 2-week titration period, ESL was administered at 400 mg, 800 mg and 1.200 mg once-daily doses for 12 weeks (in BIA 2093-303 only 800 mg and 1.200 mg).

Following these studies, eslicarbazepine acetate was approved in 2009 by the European Medicines Agency (EMA) for adjunctive therapy in adults with partial-onset seizures with or without secondary generalization. Subsequently, the results of two open-label 1 year extensions of phase III clinical trials BIA 2093-301 and BIA 2093-302 were also published (Halasz et al., 2010; Hufnagel et al., 2013).

Eslicarbazepine acetate is commercially available in Portugal since April 1st 2010. Despite good long-term safety and efficacy shown in clinical trials, there is little clinical experience with ESL and little is known about the safety and efficacy profile of this new antiepileptic drug (AED) in a day-to-day clinical setting. Our purpose was to assess the post-marketing experience with ESL in our centre, in terms of safety and efficacy profile, and ascertain whether the results were comparable to the published data.

Methods

This was an observational, single-centre, retrospective study. All the patients who initiated treatment with ESL between April 1st 2010 and October 31st 2011 at Hospital de Santo António were consecutively included.

Medical records were reviewed using a standardized form, through which data was collected on demographics (gender, date of birth), clinical features (date at epilepsy onset, diagnosis, mean number of seizures in the previous 3 months, concomitant antiepileptic drugs, antiepileptic switched for ESL), adverse events and treatment response.

All patients started treatment with eslicarbazepine 400 mg/daily for at least one week, followed by increase to 800 mg/daily. Increases from 800 mg to 1200 mg/daily and from 1200 mg to 1600 mg/daily were only made after each follow-up visit.