THIRD GENERATION ANTIEPILEPTIC DRUG MONOTHERAPIES IN ADULTS WITH EPILEPSY

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Abstract

Introduction: Drugs marketed during the last few years (i.e. Lacosamide, Ruifinamide, Eslicarbazepine acetate, Brivaracetam and Perampanel) are increasingly regarded as third generation AEDs. This paper presents available data about monotherapy with third generation drugs and on-going clinical trials with special attention to the existing debate about monotherapy license in epilepsy.

Areas covered: References were identified by searches of Medline/PubMed. In addition, currently active studies for these AEDs were identified in the ClinicalTrials.gov database.

Expert commentary: Results of studies on Eslicarbazepine acetate and Lacosamide clearly suggest good efficacy and tolerability. The selective pharmacological profile, the lack of interactions, the good tolerability with low propensity for cognitive side effects and the availability of different pharmacological formulations represent evident advantages. Although third generation monotherapies are quite promising, long-term safety data is needed in order to understand how these compounds will place in the current armamentarium.

Key words: antiepileptic drugs, epilepsy, lacosamide, eslicarbazepine acetate, brivaracetam, monotherapy, FDA, license, treatment

1. INTRODUCTION

Epilepsy is one of the most common and serious neurological conditions with incidence rates, in high-income countries, ranging between 40 and 70/100,000 persons/year, generally higher in young children and in elderly people, while in resource-poor countries the incidence is usually much higher, often above 120/100,000/year [1]. Antiepileptic drugs (AEDs) remain the mainstay of the epilepsy treatment and at least two thirds of people with epilepsy become seizure free on one or more drugs [2]. During the last two decades a new AED was launched almost annually potentially increasing the number of therapeutic options and making long-term safety a crucial point in epilepsy care. **Drugs marketed during the last few years (i.e. Lacosamide, Ruifinamide, Eslicarbazepine acetate, Brivaracetam and Perampanel) are increasingly regarded as third generation drugs** [3] because some of them (i.e. Eslicarbazepine and Brivaracetam) represent a third generation in drug improvement (**Figure 1**) and others (i.e. Rufinamide, Lacosamide and Perampanel) have new mechanisms of actions and clean pharmacological profile. In the North American literature, Clobazam and Vigabatrin are sometimes included in this list although this is probably inappropriate considering the extensive literature already published on these compounds.

In 2006, the Subcommission on AEDs guidelines of the International League Against Epilepsy (ILAE) published a review [4], updated in 2013 [5], aimed at providing an evidence-based approach to initial monotherapy in patients with newly diagnosed or untreated epilepsy (**Table 1**). This document emphasised a few major points: (i) the alarming lack of well-designed, properly conducted randomised control trials (RCTs) for patients with generalized seizures/epilepsies and for children in general; (ii) the number of methodological problems for available randomised control trials (RCTs) that limit their applicability; (iii) that the ultimate choice of an AED for any individual patient with newly diagnosed or untreated epilepsy should include consideration of all possible variables (i.e. AED safety and tolerability, pharmacokinetic properties, formulations, and expense) and not just efficacy and effectiveness. Although the ILAE document was not intended to be used for regulatory purposes, it reiterated the importance of RCTs to guide treatment choices.

Almost all AEDs obtain initial approval to be marketed through an "add-on" clinical trial design, which means adding the investigational medication or placebo to one or more baseline medications. After this step most of AEDs go through the monotherapy approval with additional studies. The majority of second generation compounds are now licensed for monotherapy, at least in the **European Union (EU**). It is, therefore, possible that most of third generation drugs will follow the same steps. **The aim of the present paper is to review available data on marketed third generation AEDs currently under Phase III for monotherapy in adults with epilepsy and to discuss current issues in the regulatory process for monotherapy**. References were identified by searches of Medline/PubMed until 30 January 2016 using the terms “monotherapy” and “Lacosamide”, “Rufinamide”, “Retigabine”, “Eslicarbazepine acetate”, “Brivaracetam” and “Perampanel”. In addition, currently active studies for these AEDs were identified in the ClinicalTrials.gov database. **Only papers published in peer-reviewed journals were included.**

2. STUDIES ON INDIVIDUAL DRUGS

There were no monotherapy studies (either published or on-going) for Rufinamide, Perampanel or Retigabine. Therefore, the paper focuses on Eslicarbazepine acetate (ESL), Lacosamide (LCM) and Brivaracetam (BRV).

2.1 Eslicarbazepine acetate

ESL is a third-generation member of a long-established family of AEDs, namely carbamazepine (CBZ) (first-generation) and oxcarbazepine (OXC) (second-generation) [6]. ESL is a pro-drug of eslicarbazepine, which is also the primary metabolite of OXC. It shares with CBZ and OXC the dibenzazepine nucleus bearing the 5-carboxamide substitute but it is structurally different at the 10,11-position. This molecular variation results in differences in metabolism and seems to be responsible for improved tolerability and ease of administration (once daily dosing). In fact, unlike CBZ, ESL is not metabolized to 10,11-epoxide and is not susceptible to induction of its own metabolism [6]. Although the precise mechanism of the anticonvulsant activity of ESL is unknown, it is thought to involve inhibition of voltage-gated sodium channels [6]. ESL has a linear pharmacokinetics and, although it does not seem to be an inducer, the **EU Summary of Product Characteristics (SPC)** recommends closely monitoring of the **International Normalised Ratio (INR)** during the first weeks after starting or stopping warfarin when prescribed in combination with ESL [6].

The **Food and Drug Administration (FDA)** has recently approved ESL as monotherapy for adult patients with partial-onset seizures in the **United States (US)** but it is still not licensed in EU. The FDA approval was based on two Phase III conversion to monotherapy trials [7,8]. Both studies were 18-week, multicentre, randomized, double-blind trials of gradual conversion to ESL monotherapy in adults with partial-onset seizures not well controlled by 1–2 AEDs. The monotherapy period was 10 weeks in both studies. Historical controls were used in both studies. One study was mainly based in North America [8] while the other one had an equal distribution between US and non-US recruitment centres [7]. In the North American study, the reduction in median standardized seizure frequency (seizures per 28 days) between baseline and the 18-week treatment period was 31% for ESL 1200 mg and 42% for ESL 1600 mg [8]. In the other study, the responder rates (a 50% or greater reduction in seizure frequency from baseline) during the 18-week double-blind period and the monotherapy period, respectively, were 35.2% and 38.9% for ESL 1200 mg, and 46.0% and 46.0% for ESL 1600 mg [7] (**Table 2**). A recently published pool analysis of these two studies provided Class IV evidence that for adults with medically uncontrolled partial-onset seizures, ESL monotherapy is well tolerated and effective [9].

In terms of safety, at least one treatment emergent adverse event (TEAE) was reported by 67% [7] and 89% [8] of patients in the two samples and in both studies mainly during the titration period with a prevalence of TEAEs in the monotherapy phase ranging between 38% and 49%. In the majority of cases, TEAEs were mild to moderate in severity and the commonest were dizziness, headache, fatigue, somnolence and nausea (**Table 3**). The discontinuation rate due to TEAEs was in the region of 7%. Changes in sodium levels were reported in around 7% of cases, no patients presented sodium levels below 125 mEq/l in the non-US study [7], while 4% reported in the North American study [8].

Two Phase III studies of ESL are currently on-going (**Table 4**). BIA-2093-311 is a double-blind, randomized, active-controlled, parallel-group, multicentre study comparing ESL with Carbamazepine Controlled Release (CBZ-CR) according to the following scheme: week 1 and 2 either 400mg/day ESL or 200mg/day CBZ-CR; Week 3 onwards either 800mg/day ESL or 400mg/day CBZ-CR. The dose would be then maintained unless a subject has a seizure and in that case the assigned treatment dose would be increased to ESL 1200mg/day or CBZ-CR 800mg/day up to ESL 1600mg/day or CBZ 1200mg/day. Subjects who remain seizure free for 26 weeks at any dose during the evaluation period will continue to receive the allocated treatment under double-blind conditions. The second Phase III trial is the open label extension phase of subjects who took part in the BIA-2093-311 trial in order to have further safety and efficacy data. These studies will allow monotherapy indication in the EU.

2.2 Lacosamide

LCM seems to have a novel mechanism of action, namely the enhancement of the slow inactivation of voltage-gated sodium channels and the modulation of the collapsing-response mediator protein 2 (CRMP-2) which seems to regulate N-type voltage-gated calcium channels, although LCM does not appear to affect N- or P/Q-type calcium channels in animal studies (10). LCM has a linear pharmacokinetics and no significant interactions are reported although the EU SPC advices advises caution with the coadministration of LCM and strong CYP2C9 (e.g. fluconazole) and CYP3A4 (e.g. clarithromycin, ketoconazole, ritonavir) inhibitors [10].

The FDA has approved LCM for the monotherapy of partial-onset seizures in patients older than 17 years in the US but it is still not available for this indication in the EU. Three published studies were identified for LCM. A Phase III, double-blind, conversion to monotherapy trial [11] and two open, conversion to monotherapy trials, one with a prospective [12] and another one with a retrospective design [13].

The first study is a historical-controlled, double-blind study of patients aged 16–70 years on stable doses of 1–2 AEDs and experiencing 2–40 partial-onset seizures per 28 days during the 8-week prospective baseline period. Patients were then randomized to LCM 400 or 300 mg/day (3:1 ratio), starting at 200 mg/day and titrated over 3 weeks to randomized dose. Background AEDs were then withdrawn over 6 weeks and patients entered a 10-week monotherapy phase. In the 400 mg/day group, 41.7% had a ≥50% reduction in seizure frequency during the 10-week monotherapy phase compared with baseline; 24.1% ≥75% reduction in seizure frequency and 14.9% remained seizure-free. The proportion of patients in the 300 mg/day group with ≥50% or ≥75% reduction in seizure frequency or who became seizure-free was comparable to that seen in the 400 mg/day group [11]. An open, single centre study in 58 patients showed that 63.8% retained LCM at 1 year from withdrawal of background AED and 32 (55.2%) remained seizure free [12]. A retrospective audit of 66 patients collected in six centres in Spain showed that two thirds of patients remained seizure free on LCM monotherapy [13] but these results are obviously of little value as this report is limited by a number of important methodological limitations such as the retrospective design and the heterogeneity of epileptic syndromes and clinical scenarios.

In terms of safety, at least 84.5% reported at least one TEAE that was mild to moderate in severity and mainly during the titration period. The commonest TEAEs were dizziness, headache and nausea. Discontinuation rate due to TEAEs was in the region of 15% [11] (**Table 3**).

In terms of on-going trials, SP0993 is already completed but results are not yet available. This is a multicentre, double-blind, double-dummy, randomized, active-controlled study comparing LCM (200 to 600 mg) to CBZ-CR (400 to 1200 mg). Patients recruited in this study will enter in SP0994 that is a multicentre, double-blind, follow up study evaluating the long-term safety of LCM in comparison with CBZ-CR with an observation phase of maximum 3.5 years. SP0994 will have an open-label, flexible-dose, extension-phase in order to collect additional monotherapy safety data. Finally, a multicentre, open-label, long-term study is investigating safety of conversion to LCM monotherapy at doses up to 600 mg in Japanese adults with partial-onset seizures.

2.3 Brivaracetam

BRV is the evolution of a family of AEDs, namely levetiracetam (LEV) and piracetam. It has a 10-fold higher affinity for the SV2A protein than LEV and, in contrast to LEV, also displays inhibitory activity on voltage-gated sodium channels [14]. BRV has a linear pharmacokinetics and no relevant interactions are reported [14].

No published studies are currently available. Two Phase III studies have just terminated NO1276 and NO1306. Both of them are double-blind, randomized, multicentre, parallel group, historical-control conversion to monotherapy studies in patients with partial-onset seizures (**Table 4**). In both cases, patients are randomised to either BRV 50 mg or 100 mg for a 17-week evaluation period. These studies have been designed to have a monotherapy license in the US.

3. DISCUSSION

Despite the large amount of data on drug refractory epileptic syndromes, studies on treatment of newly diagnosed patients with epilepsy are still limited. In fact, even large cohort studies often present data on mix of newly diagnosed and chronic patients that are obviously representative of the general population but bring limited information on outcomes of newly diagnosed patients. The SANAD trial represented a first attempt to identify pragmatic algorithms of treatment in newly diagnosed patients [15] but it was heavily criticised in terms of methodology and significance of their results [16–18].

There is general agreement that up to 49% of newly diagnosed patients with epilepsy become seizure free on their first AED and an additional 30% on a second regimen as either monotherapy or in combination with another agent [19,20]. In addition, in 60% of patients, it is possible to identify a constant course as either becoming/remaining seizure free shortly after commencing treatment or having persistent seizures despite different AED trials [20]. This data has to be considered when discussing efficacy of monotherapies with third generation AEDs as it is evident that newly diagnosed patients are more likely to respond to any treatment and what probably makes the difference is long term safety. In this regard, ESL, LCM and BRV have the advantage of a clean pharmacokinetics with a lack of interaction [3]. **In addition, preliminary studies suggest a favourable tolerability profile with no deleterious effects on cognitive functions** [21]. Further safety data is needed especially on weight gain, bone health and malformation rates during pregnancy as these variables will make the difference in terms of future success of third generation AEDs as initial monotherapies. In fact, it is now established that, although seizure freedom is an important predictor for quality of life in people with epilepsy, other factors such as mood and the adverse effects of medications are far stronger predictors [22]. In fact, although current results suggest that both LCM and ESL can be considered valuable options in newly diagnosed patients and BRV will probably produce positive results as well, how these compounds will place in the current armamentarium of treatment is far from being elucidated without long-term safety data.

The regulatory process for monotherapy license of AEDs is currently the main focus of discussion. In fact, while first generation drugs were not subjected to the regulatory standards of the FDA or the European Medicines Agency (EMA), second- and third-generation compounds have been evaluated in rigorous randomised controlled trials. As already stated, AEDs usually obtain a first regulatory approval as “add-on” but efficacy information obtained from this type of studies is not considered sufficient for monotherapy approval mainly because safety data are biased by possible interactions with concomitant medications. However, the FDA and the EMA have different views for monotherapy approval. In fact, while the FDA requires demonstration of a difference in treatment effect between the study drug and placebo or active comparator, the EMA requires therapeutic non-inferiority, or equivalence, between the study drug and a standard therapy. These differences have a number of relevant repercussions as they impose expensive obligations on pharmaceutical companies developing new AEDs in order to get a licence for monotherapy, leading to reduced investments in epilepsy research and, most importantly, a paucity of monotherapy options for patients with epilepsy. Paradoxically, while a patient with partial onset seizures who doesn’t respond

to a first AED can choose among 20 different drugs, a newly diagnosed untreated patient can choose only among a few options and this is against any tailored-treatment approach.

Both the FDA and the EMA approaches have limitations. In fact, in the FDA's view, newly diagnosed patients should be randomly assigned to the study drug or to the placebo but this is considered unethical. For this reason, studies for FDA approval have a withdrawal to monotherapy design where treatment resistant patients are converted from their existing drug to the study drug in monotherapy and their outcome compared with a virtual control group modelled from a meta-analysis of previous conversion to monotherapy studies. The unblind design is the first evident limitation but it is also important to emphasise that the comparison with historical studies completed decades ago represents another major concern as there is clear evidence for population and placebo rate changes over time [23]. Conversely, the ideal study for the EMA is a long-term, non-inferiority active control trial to a standard AED. Although this approach has a number of advantages (i.e. specific and meaningful endpoints, active comparator, individualized treatment), it is evident that this design per se cannot distinguish between effective and ineffective treatments and cannot exclude that a placebo would have behaved similarly. In fact, according to this approach, two equally weakly effective or ineffective treatments would perform similarly and this is even more relevant in monotherapy studies as up to 50% of newly diagnosed patients become seizure free on their first treatment.

Although there is general agreement that different licensing mechanisms for adjunctive treatment and monotherapy are not supported by any clinical and scientific rational, it must be acknowledged that without monotherapy trials, clinicians may use new drugs in newly diagnosed patients without enough time to identify serious adverse events that are usually identified after a large number of patients are exposed. This specific issue could be potentially overcome encouraging post-authorisation Phase IV studies in a sequential licensing process and the advantages of this process have been clearly identified [23,24]. It is evident that a unified protocol for monotherapy indication of AEDs is urgently needed as well as properly-designed studies to implement evidence-based guidelines of treatment of newly diagnosed patients with epilepsy.

4. CONCLUSIONS

Current studies suggest that ESL, LCM and possibly BRV, will be valuable options for the initial monotherapy of patients with localization-related epilepsies. The low impact on cognitive functions, the lack of pharmacokinetic interactions and the selective pharmacological profile represent important advantages. Long-term safety data from Phase IV studies are needed especially regarding, weight gain, bone-health and malformation rates. New policies for monotherapy license for AEDs are needed in order to promote further research into epilepsy treatments.

5. EXPERT COMMENTARY

Results of studies on ESL and LCM clearly suggest good efficacy and tolerability. The selective pharmacological profile, the lack of interactions and the good tolerability with low propensity for cognitive side effects represent evident advantages. In addition, in the case of LCM, different formulations are available (i.e. tablets, liquid oral solution and liquid intravenous solution), offering a wide range of applications in different clinical scenarios. It is quite likely that BRV will be as successful as ESL and LCM in the withdrawal to monotherapy studies and will be licensed for monotherapy in the US but studies are still on going. In this regard, it is becoming evident that new policies for the monotherapy indication of AEDs are urgently needed in order to offer as many options as possible to patients with newly diagnosed epilepsies. This is particularly important for

generalised epilepsy syndromes where the number of licensed drugs is quite limited and some drugs are burdened by unacceptable side effects (i.e. valproate in women of child bearing age). It has to be admitted that pharmaceutical companies are progressively leaving the epilepsy field because of these somehow byzantine regulatory protocols and this is not acceptable for the many patients developing epilepsy every year that are entitle to have better and better options in terms of efficacy, tolerability, long-term safety and easy ways of administration. The proposal of a sequential licensing process based on Phase IV studies represents an interesting option to have clear safety data and to simplify the license process at the same time.

6. FIVE YEARS VIEW

Third generation AEDs showed clear advantages in terms of selective mechanisms of action, lack of side effects on cognitive functions and lack of interactions. Most of them are already licensed for monotherapy in US (i.e. ESL and LCM) and they will be probably available in Europe for monotherapy as well. Current data suggests that these AEDs have a low propensity for side effects and are generally well tolerated. The titration regime is quite simple for all of them and this represents another important advantage. Previous AEDs, such as LEV, that showed a similar balance between efficacy and safety, became rapidly popular in the epilepsy treatment. For this reason, it is possible to hypothesize that they will also become increasingly popular and widely prescribed if major safety issues do not come up. LCM and BRV are also available for the intravenous administration being an important option in the acute setting. While in the EU there are a number of AEDs already licensed for monotherapy, in the US mainly first generation AEDs are available. Therefore, it is possible to hypothesis that they will become extremely popular in the US market. As long-term safety represents an important variable for monotherapies in epilepsy, data from pregnancy registers and Phase IV studies will clearly decide on the success of third generation AEDs for newly diagnosed patients.

7. KEY ISSUE

- Lack of significant drug-drug interactions, life-threatening adverse events and negative impact on cognition are significant advantages of third generation antiepileptic drugs
- Data on monotherapy are available for LCM and ESL while for BRV trials are currently on going
- LCM and ESL are already licensed for monotherapy in US
- Available studies suggest good efficacy and tolerability for LCM and ESL but long term safety data is needed especially regarding teratogenicity, bone health and weight gain

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FIGURE LEGEND

Figure 1. Examples of the three generations antiepileptic drugs.