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Abstract

Objective: Perampanel (PER) has been shown to be effective as an adjunctive therapy for controlling refractory focal-onset seizures (FOS). However, the information as early add-on for the treatment of FOS in the clinical practice is still scarce and must be further assessed.

Methods: An observational prospective study was conducted to evaluate the effectiveness of early add-on PER, assessed as 50% responders (seizure frequency reduced by at least 50% during the last 3 months as compared with baseline) rate at 6 and 12 months, in patients with FOS in the routine clinical practice of Spain.

Results: One hundred and thirteen patients (mean age: 40.3 years, 51.3% male) with FOS received PER as early add-on (1st add-on: 37.2% and 2nd: 62.8%) for a mean exposure of 11 months (mean PER dose: 6.3 mg/day at month 12).

At 6 months, 50.4% and 20.4% of the patients were responders and seizure-free (respectively) relative to baseline (3 months prior to PER initiation), and at 12 months, 68.1% and 26.5% of the patients were responders and seizure-free (respectively), relative to baseline (3 months prior to PER initiation). The retention rate at 6 and 12 months was 83.2% and 80.5%, respectively. The percentage of seizure-free patients at 12 months was significantly (p = 0.033) higher when PER was added as first vs. second add-on. The number of concomitant antiepileptic drugs (AEDs) was significantly reduced from baseline to 6 and 12 months (p = 0.001). Treatment was simplified in 23.9% of patients at the end of the observation period. Drug-related adverse events (AEs), most mild or moderate, were reported in 30.1% of patients, with irritability (8%) and dizziness (7.1%) as the most frequent ones.

Conclusions: This is the first observational, prospective study to evaluate efficacy and safety of early adjunctive treatment with PER in patients with focal epilepsy at 12 months. Perampanel demonstrated a good efficacy and safety profile when used at a median dose of 6 mg/day, regardless of the combination with other AEDs. Adverse events were mild or moderate, with dizziness being the most frequent one.

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Keywords: Perampanel; Epilepsy; Antiepileptic drug; Early add-on; Focal-onset seizures

Abbreviations: AED, antiepileptic drug; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CBZ, carbamazepine; CNS, central nervous system; CPS, complex partial seizure; DRE, drug-refractory epilepsy; EMA, European Medicines Agency; ESL, eslicarbazepine acetate; FAS, focal aware seizures; FBTCs, focal to bilateral tonic–clonic seizures; FAS, focal impaired awareness seizure; FOS, focal-onset seizures; IGE, idiopathic generalized epilepsy; ILAE, International League Against Epilepsy; LCM, lacosamide; LEV, levetiracetam; LOCF, last observation carried forward; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PER, perampanel; PGTC, primary generalized tonic–clonic; PHT, phenytoin; SCB, sodium channel blocker; SD, standard deviation; TEAEs, treatment-emergent adverse events; TPM, topiramate; VPA, valproic acid.

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1. Introduction

Epilepsy is one of the most common neurological diseases and accounts for 5% of the proportion of total disability-adjusted life years (DALYs) for all the neurological conditions [1]. To this day, about 70% of people living with epilepsy achieve seizure freedom when seizures are properly diagnosed and treated [2], but about 30% (22.7% in Spain) become refractory to treatment [3,4]. Drug-refractory epilepsy (DRE) is associated with decreased quality of life and increased hospitalization, morbidity, and mortality rates, being, in addition, treated with polytherapy [5,6].

Although polytherapy with antiepileptic drugs (AEDs) may be associated with more adverse events (AEs) [7–9], it has been demonstrated that the burden of AEs is likely to be related more to type of AEDs/AED combination than to the number of coprescribed AEDs or AED load [10]. Rational polytherapy combining AEDs with different mechanism of action (MOA) has produced some improvement in prognosis [11,12]. In patients with uncontrolled epilepsy by the initial AED, practice has evolved to a bitherapy with an AED with different MOA [13]; thus, recent AEDs with new MOAs are being developed to control epileptic seizures by acting on different targets than those commonly used by previous AEDs.

Perampanel (PER) is a first-in-class noncompetitive selective antagonist of the α-ami-no-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor [14], the main postsynaptic receptors for glutamate, which is crucial in triggering and spreading epileptic activity [15]. As PER has a unique MOA [14], it has the potential to control seizures, which have not been controlled by previous AEDs. In phase III studies, adjunctive PER therapy has shown to be effective for controlling refractory focal-onset seizures (FOS) [according to the 2017 Epilepsy classification from the International League Against Epilepsy (ILAE) nomenclature] [16], with or without focal to bilateral tonic-clonic seizures (FBTCS), over placebo, as well as safe and acceptably tolerated in randomized clinical trials at doses of 4, 8, and 12 mg/day [17–19], with extension studies showing its efficacy and tolerability up to 4 years [20–22]. In the routine clinical practice, there are several studies that have confirmed PER effectiveness for controlling FOS but these studies are mostly retrospective [23–25] (which impede the higher accuracy of data collection with regard to exposures, confounders, and endpoints [26]), and use PER mainly as late add-on [23–25,27].

The European Medicines Agency (EMA) authorized PER in 2012, with indication for the adjunctive treatment of partial-onset seizures, with or without secondarily generalized seizures, in patients 12 years of age with epilepsy and for the adjunctive treatment of primary generalized tonic–clonic (PGTC) seizures in patients from 12 years of age with idiopathic generalized epilepsy (IGE) [28,29] (indication terminology based on ILAE 1989 Epilepsy Classification) [30].

Since data from PGTC in patients with IGE (also known as genetic generalized epilepsy) suggest that PER early add-on might lead to better efficiency results than late add-on [31], it was of interest to find out how the use of PER as early add-on could impact on its effectiveness to control FOS in the clinical practice. With this aim in mind, a prospective study was conducted.

2. Material and methods

An observational prospective study was conducted to evaluate the effectiveness of PER as early add-on (first or second add-on) in patients with FOS in the routine clinical practice at 6 and 12 months after treatment initiation.

Participant hospitals are considered of secondary and tertiary level in the region of Andalusia (Spain), being the majority general neurology consultations. The decision to prescribe PER was made by the treating physician based on clinical need and suitability.

2.1. Patient population

Recruited patients were ≥12 years, had a clinical diagnosis of epilepsy with noncontrolled FOS (with or without FBTCS), according to the 2017 ILAE classification [16], and the physician had decided to initiate treatment with PER as 1st or 2nd adjunctive AED in the routine clinical practice. In addition, patients had to be reliable to participate in the study for the whole study period and able to register the seizures and possible AEs. Exclusion criteria included the following: patients with a history or clinical evidence of previous psychiatric or affective disorder and/or previous antipsychotic drug use or suicide attempt in previous 2 years, any progressive central nervous system (CNS) disorder including degenerative disorders and progressive oncologic disease –, and pregnant or lactating women.

Study visits were planned at 6 and 12 months, coinciding with usual visits in addition to baseline visit, and data were entered into a Case Report Form (CRF). No intervention was applied; patients had to record their seizures in their written diaries, and data were entered by the clinician into the CRF. Adverse events were not recorded by patients in their seizures diaries but collated into the CRF by the investigator at the 6- and 12-month visits, when patients were interviewed.

We considered that PER was added as 1st add-on when it was added to patients that were suffering from FOS despite treatment with monotherapy of an approved AED; thus, PER was added as the second AED. (These patients had not had any other previous AED monotherapy).

We considered PER was added as 2nd add-on when it was added to patients that were suffering from FOS despite treatment with bitherapy (two approved AEDs) and thus, PER was added as the third AED. (These patients had not had any other previous treatment than the two AEDs they were on at the time of PER addition).

All enrolled patients signed an informed consent. The study was approved by the Clinical Research Andalusia Regional Ethics Committee, and it was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

2.2. Primary endpoint

The primary endpoint was assessed by means of the 50% responders’ rate; patients were considered responders when mean number of seizures was reduced by at least 50% at months 6 and 12, relative to baseline (mean number of seizures occurred within the 3 months prior to baseline visit).

2.3. Secondary endpoints

The study also intended to determine the seizure freedom rate at 6 and 12 months after treatment initiation. Seizure freedom was defined as number of patients who achieved seizure freedom relative to baseline (3 months prior to baseline visit), which for both, the 6- and 12-month visit meant no seizures since baseline visit. Retention rate (defined as the proportion of patients reaching the end of the study on treatment with PER) at 6 and 12 months was also analyzed. The proportion of patients with seizures, the number of seizures per month, and the reduction of the mean number of seizures per month, for focal aware seizures (FAS), focal impaired awareness seizure (FIAS), and FBTCS, was also determined. Other secondary objectives were to assess safety by recording the AEs occurred at 6 and 12 months. Study withdrawals due to AEs were also gathered.

The following subanalyses (50% responder rate, seizure freedom, AEs rate, and retention rate) were also carried out, and comparisons between subgroups according to two variables were performed: PER add-on therapy (first vs. second add-on therapy) and MOA of coconitant AEDs [sodium channel blocker (SCB) vs. no SCB]. The following AEDs were considered SCB: eslicarbazepine acetate (ESL), carbamazepine (CBZ), oxcarbazepine (OXC), lacosamide (LCM), lamotrigine (LTG), and phenytoin (PHT).
2.4. Statistical analysis

A descriptive analysis was conducted. Qualitative variables were assessed by absolute and relative frequencies, and quantitative variables by measurements of central tendency [mean, standard deviation (SD), median, minimum and maximum values, 95% Confidence Interval (CI), or P25-P75] and number of valid cases. Time to event was assessed by Kaplan–Meier curves. Intergroup comparisons were performed by the Chi-squared or the exact Fisher test for qualitative variables and by the Student t or Mann–Whitney U-test for the quantitative variables.

For retention rates, the patient percentages that continued on treatment at 6 and 12 months were reported.

Patient response (seizure-free and ≥50% responders’ rate) was described as absolute and relative frequencies. The change in seizure number from baseline was assessed by the Wilcoxon test, and the patient percentage change in seizure type from baseline was assessed by the McNemar test. Last observation carried forward (LOCF) was used for missing data.

Simplification included reduction from three to two or one AED or from two to one AED (switch to PER monotherapy).

The presence/absence, severity, and type of AEs were described by absolute and relative frequency.

For subgroup analyses, baseline characteristics were assessed by the Student t-test (or the Mann–Whitney U-test) and by means of the Chi-squared test (or Fisher exact test) according to the type of variables. The analyses of efficacy and safety were performed by means of the Chi-squared test (or Fisher exact test). The analysis according to PER titration was only conducted for the slow and rapid groups; the “other” group was excluded since it included very diverse ways of titrating the drug [rapid (dose increase of 2 mg a week), slow (dose increase of 2 mg every 2 or more weeks), and other titration].

The sample size to assess the main objective was estimated as 150 patients, considering a PER response of 31% with a precision of ±8%, based on pivotal studies [17–19], accepting an alpha risk of 0.05 in a bilateral contrast, and considering a maximum loss of 5% of patients for not meeting inclusion/exclusion criteria.

The significance level was set at 5%. The SPSS software was used for all analyses.

3. Results

A total of 113 patients diagnosed of epilepsy and suffering from uncontrolled FOS were enrolled. Patients’ disposition is shown in Fig. 1. Age ranged from 12.9 to 79.1 years (mean: 40.3 ± 17; 71.1% 65 years or older), and 51.3% of patients were male. At treatment initiation, many patients had relevant comorbidities, and the mean number of FOS, with or without FBTCS, per month was 2.6. At baseline, all patients had at least one FOS (Table 1).

Perampanel was added as 1st add-on in 37.2% (added to monotherapy with 1 AED) of patients and as 2nd add-on in 62.8% (added to a combination of 2 AEDs). At 6 months, the retention rate with PER was of 94 (83.2%) patients and 91 (80.5%) at 12 months. Treatment was withdrawn from 22 of the 113 initial patients, mainly due to AEs (15.9%), and the mean time of PER exposure was 11 months (95% CI 11.0–12.7).

The median PER dose at treatment initiation was 2 (min–max, 2–4) mg/day and was titrated up to a median dose of 6 (4–12) mg/day at 6 and at 12 months. Dose titration was slow in 60.7% of patients, rapid in 17%, and not defined in 22.3%.

If the ‘not defined titration’ group of patients was excluded (n = 26) and the rest divided into those in which PER titration was done rapidly (21.8%) or slowly (78.2%), retention rates in the slow titration group at 6 and 12 months were 89.7% and 86.8%, respectively, and 52.6% in the rapid titration group at both time points. The proportion of patients with treatment-related AEs was 23.5% and 52.6% in the slow and rapid titration groups, respectively, and the percentage of patients who withdrew treatment with PER was 10.3% and 47.4% in the slow and rapid titration groups, respectively.

The most common concomitant AEDs were levetiracetam (LEV; 36.3%), ESL (25.7%), and LCM (22.1%) (Suppl. Table 1).

3.1. Effectiveness

The responders’ rate for all FOS was 50.4% at 6 months and 68.1% at 12 months. At 6 months, 20.4% of patients were seizure-free, and at 12 months, the percentage reached 26.5% (Fig. 2).

Percentage of patients with FOS, FAS, FIAS, and FBTCS and evolution of the median number of seizures per month at 6 and 12 months relative to baseline are stated on Table 2.

3.2. Concomitant AEDs evolution

In our population, the total number of concomitant AED was significantly reduced from baseline [median 2 (min–max: 1–3)] to 6 and 12 months [median 1 (min–max: 0–3)]; p = 0.001 at both time points. At the end of the observation period, treatment was simplified in 23.9% of patients, and 4.4% had been converted to PER monotherapy. The dose of concomitant AEDs at baseline and at the end of the observation period is shown in Suppl. Table 2.

3.3. Safety

Thirty-four patients (30.1%) showed treatment-related AEs (10.6% mild, 15% moderate, and 4.4% severe), none of which was a serious adverse event (SAE). The most frequent AEs were irritability (8%), dizziness (7.1%), and behavior disorder (4.4%) (Table 3).

Twenty-three patients (20.4%) showed at least one drug-related psychiatric AE (8.8% mild, 8.8% moderate, and 2.7% severe). The most frequent ones were irritability (8%), followed by behavior disorder (4.4%) and aggressiveness (3.5%) (Table 3).

Treatment was discontinued due to AEs in 15% of patients at 6 months and in 15.9% at 12 months. Looking specifically at psychiatric AEs, by the end of the observation period, 11 patients (9.7%) had discontinued treatment because of this type of AEs: Agitation 1, aggressiveness 3 (1 also due to weight increase), depression 1, irritability 1, and behavior disorder 5.
3.4. Groups according to the mechanism of action of concomitant AEDs

When the sample was divided into patients with SCBs as concomitant AEDs (69.9%) and with AEDs other than SCBs (30.1%), no statistically significant differences were found in efficacy and safety variables.

When the sample was divided into patients on treatment with PER + LEV (36.3%) or PER without LEV (63.7%), no significant differences were observed in demographic variables, retention rates, and efficacy variables (seizure freedom and responder rates) at 6 and 12 months. Furthermore, no significant differences were found among safety variables, including the proportion of patients with treatment-related AEs, psychiatric AEs, and withdrawals due to AEs.

4. Discussion

Perampanel has been previously shown to be effective as adjunctive therapy for controlling refractory FOS, with or without FBTCs while being safe and acceptably tolerated [17–20]. However, this is the first prospective study conducted to obtain real-world effectiveness and safety data of PER used as first or second add-on for FOS. Real-world data are collected in the course of routine healthcare delivery and provide valuable insight into treatment effectiveness and safety in day-to-day clinical practice, complementing the data from Randomized Clinical Trials (RCTs), which were obtained under strict inclusion and exclusion criteria [32,33], thus, the importance of the current study.

4.1. Effectiveness

At 12 months, the 50% responders’ rate in our study was 68.1% and 26.5% of patients were seizure-free, relative to baseline. In clinical trials, PER has a dose–response effect, at least up to 8 mg [18,19], and yet in our prospective study, these high rates were achieved with a low median dose of 6 mg/day; thus, the most likely explanation for the high

Table 1
Patients baseline characteristics.

<table>
<thead>
<tr>
<th>Categories</th>
<th>Total N =</th>
<th>1st add-on</th>
<th>2nd add-on</th>
<th>p-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>39.8</td>
<td>42.5</td>
<td>38.9</td>
<td>0.283</td>
</tr>
<tr>
<td></td>
<td>[32.9–79.1]</td>
<td>[37.3–47.7]</td>
<td>[34.8–43.0]</td>
<td></td>
</tr>
<tr>
<td>≥65 years</td>
<td>8 (7.1%)</td>
<td>3 (7.1%)</td>
<td>5 (7.0%)</td>
<td>0.629</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25 (51.3%)</td>
<td>24 (57.1%)</td>
<td>34 (47.9%)</td>
<td>0.341</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>164.7 ± 10.5</td>
<td>163.6 ± 9.5</td>
<td>165.3 ± 9.6</td>
<td>0.715</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>10.5</td>
<td>12.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No alcohol consumption</td>
<td>94 (98.9%)</td>
<td>39 (97.5%)</td>
<td>55 (100.0%)</td>
<td>0.421</td>
</tr>
<tr>
<td>Relevant comorbidities</td>
<td>69 (61.1%)</td>
<td>23 (54.8%)</td>
<td>46 (64.8%)</td>
<td>0.291</td>
</tr>
<tr>
<td>CNS or sensory organs</td>
<td>16 (14.2%)</td>
<td>4 (9.5%)</td>
<td>12 (16.9%)</td>
<td>0.212</td>
</tr>
<tr>
<td>Musculoskeletal system</td>
<td>4 (3.5%)</td>
<td>1 (2.4%)</td>
<td>3 (4.3%)</td>
<td>0.524</td>
</tr>
<tr>
<td>Skin and subcutaneous tissues</td>
<td>4 (3.5%)</td>
<td>0 (0.0%)</td>
<td>4 (5.6%)</td>
<td>0.151</td>
</tr>
<tr>
<td>Hematologic system</td>
<td>2 (1.8%)</td>
<td>0 (0.0%)</td>
<td>2 (2.8%)</td>
<td>0.393</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>2 (1.8%)</td>
<td>2 (4.8%)</td>
<td>0 (0.0%)</td>
<td>0.136</td>
</tr>
<tr>
<td>Digestive system</td>
<td>1 (0.9%)</td>
<td>0 (0.0%)</td>
<td>1 (0.4%)</td>
<td>0.634</td>
</tr>
<tr>
<td>Genitourinary system</td>
<td>1 (0.9%)</td>
<td>1 (2.4%)</td>
<td>0 (0.0%)</td>
<td>0.372</td>
</tr>
<tr>
<td>Other</td>
<td>24 (21.2%)</td>
<td>7 (16.7%)</td>
<td>17 (23.9%)</td>
<td>0.361</td>
</tr>
<tr>
<td>Epilepsy evolution time</td>
<td>4.4</td>
<td>4.7</td>
<td>4.4</td>
<td>0.850</td>
</tr>
<tr>
<td>FOS/month at treatment initiation</td>
<td>1.2 (0.2–25.3)</td>
<td>1.0 (0.2–25.3)</td>
<td>1.7 (0.2–15.8)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

BMI: body mass index; CV: cardiovascular; CNS: central nervous system; FAS: focal aware-ness seizures; FIAS: focal impaired awareness seizures; FBTCs: focal to bilateral tonic-clonic seizures.

Qualitative data expressed as n (%).
Quantitative data expressed as mean ± SD or median [range].
Bold numbers: Significant p-values.
* One patient may present more than 1 comorbidity.
† Data were available only for a total of 90 patients.
‡ All patients had at least one FOS at baseline.
§ p-Values of the comparison of characteristics between first and second add-on groups.

Treatment was discontinued due to lack of efficacy in 0.9% and 2.7% of patients at 6 and 12 months, respectively.

3.4. Groups according to the use of PER as first or second add-on

A subanalysis was made to compare treatment with PER as first (37.2% of patients) or as second add-on (62.8%). Although both groups had broadly similar demographic and clinical characteristics, the following significant differences were found between them: At baseline, the number of seizures/month was greater in the 2nd add-on than in the 1st add-on group [median 1.7 (0.2–15.8) vs. 1 (0.2–25.3); p = 0.004], and the proportion of patients with FAS was higher in the 1st than in the 2nd add-on group (38.1% vs. 12.7%; p = 0.002). In addition, the number of FAS/month [median 1.8 (0.2–15) vs. 0.7 (0.2–12); p = 0.001] and that of FBTCs/month [0.5 (0.2–13.3) vs. 0.3 (0.2–0.8); p = 0.001] were higher in the 2nd add-on than in the 1st add-on group.

At 12 months, the proportion of seizure-free patients was significantly higher when PER was added as 1st vs. 2nd add-on (38.1% vs. 19.7%; p = 0.033) (Fig. 2), and the proportion of patients that simplified treatment was significantly greater when PER was added as 2nd vs. 1st add-on (35.2% vs. 4.8%; p < 0.001). No statistical differences were found in the responders’ rate and retention rate at 6 and 12 months.

The proportion of patients with AEs (36.6% vs. 19%; p = 0.049) and with psychiatric AEs (28.2% vs. 7.1%; p = 0.008) were significantly higher when PER was added as 2nd add-on, as compared with the 1st add-on.
The efficacy observed was the early use of PER as first or second add-on. Our results are in line with a previous study conducted in patients with IGE that showed that significantly (p = 0.020) more patients achieved seizure freedom from all seizures when PER was used as early add-on (PER that showed that significantly reduced at 12 months relative to baseline [31]. Treatment simplification will allow fewer complex regimes, allowing higher adherence rates and thus, having less seizures due to missed doses [37].

4.2. Safety

In our study, PER has shown a good tolerability profile in routine clinical practice, comparable with that shown in clinical trials, with no new or unexpected AEs. Thirty percent of patients experienced at least one drug-related AE, while previous studies conducted in the routine clinical setting have shown rates of 50 to 65% at 12 months [24,25,31,38,39]. The lower incidence of AEs in our study might be explained by the low PER dose maintained (median: 6 mg/day), since higher doses are associated with higher incidence of AEs [40]. Furthermore, and since the proportion of patients with AEs was significantly lower in the 1st than in the 2nd add-on group, the early use of PER in our study might also have to do with the lower treatment-emergent adverse events (TEAEs) rate observed. A previous Spanish study with a median of 6.8 AEDs prior to PER still showed a low percentage of AEs (35.5%) [36]. Possible reasons for this were the slow titration scheme used and the lack of systematic questionnaire to report AEs.

The prevalence of psychiatric and behavioral adverse reactions in patients with epilepsy has been estimated to be 8–20% and 11–14% in patients ≤18 years [41]. Our study showed 3.5% of aggressiveness that even added to irritability (8%) or behavior disorders (4.4%) is a lower percentage than those observed in previous clinical studies (18–24% for aggressiveness and/or irritability) [23–25,39]. Aggression has been shown to be higher in adolescents than in adults [42], which might explain the high percentage of aggressiveness observed in the studies with a high percentage of adolescents [24,39]; median age of patients in our study was 39.8. Another explanation for the lower rates of aggressiveness and/or irritability observed in our study might be based on PER dose. A recent 12-week prospective study suggests that PER increases aggression with a dose-dependent effect [43]; thus, the lower PER dose maintained in our study at a median of 6 mg/day might partly explain the lower aggressiveness shown. Keeping PER dose at lower levels might be part of the management strategy to reduce AEs, especially when patients present with risk factors for AED-induced psychotropic effects (female sex, psychotic disorder comorbidities, polytherapy with AEDs, and the duration of epilepsy) [9].

In routine clinical practice, the treatment with PER or LEV has been associated with AEs such as irritability and aggression [41], but the efficacy and AEs reported in patients whose seizures were treated with PER
and LEV have not yet been fully investigated [44]. In the current study, no differences were observed regarding AEs, psychiatric AEs, or PER withdrawal whether LEV was used or not, which suggests that concomitant use of LEV with PER does not increase the likelihood of AEs, and specifically the likelihood of psychiatric AEs. In a study conducted in 39 patients with DRE with mean age of 13.7 years, the concomitant use of LEV with PER seemed to be more effective than PER without LEV and did not show any increase in overall AE frequency, although aggression was present in 2 patients on PER treatment without LEV and in none with concomitant LEV [44]. Similar efficacy and safety data were observed in the current study.

Seventy percent of patients were on treatment regimens including SCBs, since they have been the mainstay of the pharmacological management of FOS for more than 70 years and still have an important place in epilepsy management [45]. The current study showed similar effectiveness and safety results when PER was used in patients receiving SCB or not receiving SCB, in agreement with the FYDATA Study [34], where no significant differences were found in AE frequency in patients receiving and not receiving SCB.

There was a higher proportion of patients with drug-related AEs and a higher withdrawal due to AEs in the rapid than the slow titration group, thus, the higher retention of patients in the slow titration group. These data support a slow titration of PER (increase of 2 mg every 2 weeks). As opposed to these findings, two previous studies did not find significant differences in overall AEs between the slow and rapid titration groups [25,39]. However, a different definition for slow (2-mg increments at intervals of 3 weeks or longer) and rapid titration (2-mg increments at intervals of 1 to 2 weeks) was used, with their rapid definition overlapping our slow definition, which might explain their results.

Limitations of this study include those inherent to observational studies but, as opposed to most current clinical studies with PER, which are retrospective, this is a prospective study; thus, the associations between PER exposure and outcomes are more rigorous. Another limitation could be the fact that AE frequency could have been underestimated, because of the lack of systematic AEs reporting.

4.3. Conclusions

This is the first observational, prospective study to evaluate efficacy and safety of early adjunctive treatment with PER in patients with focal epilepsy at 12 months. Perampanel demonstrated a good efficacy and safety profile when used at a median dose of 6 mg/day, regardless of the combination with other AEDs. The proportion of seizure-free patients was greater when patients’ seizures were treated with PER as first versus second add-on. Adverse events were mild or moderate, with dizziness being the most frequent one.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2019.106655.

References


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