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Perampanel effectiveness and safety as early add-on treatment for focal-onset seizures: PEREAGAL study

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ABSTRACT

Background: Perampanel (PER) is an effective adjunctive therapy for controlling focal-onset seizures (FOS), but few studies have examined its effects as an early add-on for the treatment of FOS in daily clinical practice.
Methods: Our retrospective, multicenter, observational study evaluated the effectiveness and safety of PER as an early add-on in 77 patients with FOS, with and without focal to bilateral tonic-clonic seizures (FBTCS) after 3, 6 and 12 months in a real-world setting.
Results: After 12 months of treatment (median dose 6 [4,8] mg/day), the retention rate was 79.2 % and 60 % of patients (39/65) experienced a ≥50 % reduction in seizure frequency relative to baseline. The seizure-free rate was 38.5 % for all seizures (25/65) and 60 % for FBTCS (12/20). The responder rate at 12 months was significantly higher when PER was given with one concomitant AED (72.2 %) compared to when PER was given with two concomitant AEDs (44.8 %). Drug-related adverse events (AEs) were reported in 40.3 % of patients, most of them being mild (64.2 %). Twelve patients (15.6 %) discontinued treatment because of AEs.
Conclusions: PER is an effective and safe early add-on for patients with refractory FOS, especially for those with FBTCS.

1. Introduction

Around 30 % of patients with epilepsy fail to respond to antiepileptic drugs (AEDs) (Chen et al., 2018). When monotherapy fails to control patients' seizures, it is common clinical practice to add a second or third AED as concomitant therapy. Many factors influence the choice of an early add-on treatment (Ben-Menachem, 2014; Sánchez-Álvarez et al., 2012; French et al., 2004), but robust evidence to guide clinicians is lacking. "Rational polytherapy" supports the combination of AEDs with different mechanisms of action to maximize efficacy and minimize adverse events (AEs) (Chi et al., 2018; Brodie and Sills, 2011).

Perampanel (PER) is a first-in-class, selective, non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) postsinaptic receptor antagonist (Tsai et al., 2018). Once-daily PER (4–12 mg) is approved in Europe as adjunctive therapy for patients with focal seizures, with or without secondary generalization, over 12 years of age. Some anti-epileptic drugs known as enzyme inducers (carbamazepine, phenytoin, oxcarbazepine) have been shown to increase perampanel clearance (European Medicines Agency, 2020).

PER's unique mechanism of action, wide spectrum of activity and once-daily dosage, makes it an attractive early add-on treatment option. However, few studies have examined its effectiveness in clinical practice (Abril Jaramillo et al., 2020; Kim et al., 2018; Shah et al., 2016). This retrospective, multicenter, observational study evaluated the

Abbreviations: AEs, adverse events; AEDs, anti-epileptic drugs; FBTCS, focal to bilateral tonic-clonic seizures; FOS, focal-onset seizures; PER, perampanel.

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effectiveness and safety of PER as an early add-on in patients with focal-onset seizures (FOS), with and without focal to bilateral tonic-clonic seizures (FBTCS), after 3, 6 and 12 months.

2. Methods

2.1. Study design and patients

We carried out a retrospective, observational study involving epilepsy specialists in 6 hospitals in Galicia, Spain, to evaluate the effectiveness and tolerability of PER as an early add-on in 77 patients with FOS after 3, 6 and 12 months in a real-world setting.

The study protocol was approved by the Galician Ethics Committee and followed the Declaration of Helsinki code of ethics. Inclusion criteria were: ≥ 12 years of age; diagnosed with focal-onset epilepsy according to the 2017 ILAE classification (Fisher et al., 2017), concomitantly treated with 1–2 AEDs and who have previously received 0–2 AEDs; and signed an informed consent form. Patients with inaccurate or unreliable clinical records according to participating physicians were excluded.

Information on the following variables was collected from patient records: age, age at onset of epilepsy, sex, aetiology and localization of epilepsy, type of seizures, psychiatric comorbidities, prior AEDs, concomitant AEDs, reasons for starting PER, adverse events, PER dose and reasons for abandoning PER. Concomitant AEDs were classified by main mechanism of action and enzyme-inducing capacity.

2.2. Endpoints

We assessed the effectiveness of PER as an early add-on as the percentage of patients achieving ≥50 % reduction in seizure frequency (responder rate) and the percentage of patients achieving seizure freedom.

Patients were considered responders when the mean number of seizures was reduced by at least 50 % at months 3, 6 and 12, relative to baseline (the 3-month period prior to PER initiation).

Seizure freedom at every time point was defined as no seizures since the prior visit, thus seizure freedom at 12 months was defined as no seizures during the 6 months prior, whereas seizure freedom at 3 and 6 months were defined as no seizures since baseline or 3- month visit, respectively.

We also determined the effectiveness of PER on different seizure types (focal aware seizures motor and non-motor, focal impaired awareness seizures, and FBTCS). We calculated the retention rate, defined as the proportion of patients that reach the end of the study's observation period on PER treatment, and evaluated the tolerability of PER as an early add-on as the percentage of patients experiencing AEs and that discontinue treatment due to AEs at 3, 6 and 12 months.

2.3. Statistical analysis

Quantitative variables were described by measurements of central tendency (mean, standard deviation, median and interquartile range). Qualitative variables were described by absolute frequencies and percentages. Intergroup comparisons were performed by the Chi-square test or the exact Fisher test for qualitative variables and by the Student t-test or the Mann–Whitney *U* test for quantitative variables. Time to event was calculated with Kaplan–Meier curves. The change in seizure number from baseline was assessed by the Wilcoxon test, and the patient percentage achieving seizure freedom from baseline was assessed by the McNemar test. The multivariate modeling of the responders was carried out by binary logistic regression, with the dependent variable being the response to the treatment, and additionally the presence of AEs. The independent variables examined include: baseline characteristics, prior and concomitant AEDs (number, mechanism of action, and enzyme-inducing capacity). All statistical analyses were performed using SPSS version 22.0 (IBM Corporation, Armonk, NY, USA). The threshold of significance was $p < 0.05$.

Table 1
Patient baseline characteristics (n = 77).

Male / Female, n (%)	45 (58.4 %) / 32 (41.6 %)
Median age [IQR]	46 [33–58.5] years
Patients over 65 years	13 (16.8 %)
Median age at epilepsy onset (IQR)	31 [15–48] years
Type of epilepsy, n (%)	
Tumoral	10 (13 %)
Vascular	9 (11.7 %)
Mesial Temporal Sclerosis (MTS)	7 (9.1 %)
Brain Traumatic Injury	5 (6.5 %)
Cavernoma	3 (3.9 %)
Unknown	34 (44.2 %)
Other	9 (11.7 %)
Type of seizure (baseline visit), n (%)	
Focal impaired awareness seizure (FIAS)	46 (55.4 %)
Focal to bilateral tonic–clonic seizures (FBTCS)	25 (30.1 %)
Focal onset aware motor seizures	6 (7.2 %)
Focal onset aware non-motor seizures	6 (7.2 %)
Psychiatric comorbidities, n (%)	
≥ 1 psychiatric comorbidity	25 (32.5 %)
No psychiatric comorbidities	52 (67.5 %)
Prior AEDs, n (%)	
No prior AED	36 (46.8 %)
1 prior AED	28 (36.4 %)
2 prior AEDs	13 (16.9 %)
Most common prior AED:	
Levetiracetam	14 (18.2 %)
Carbamazepine	9 (11.7 %)
Phenytoin	7 (9.1 %)
Valproic Acid	6 (7.8 %)
Concomitant AEDs, n (%)	
Currently taking 1 AED	46 (59.7 %)
Currently taking 2 AEDs	31 (40.3 %)
Most common concomitant AED:	
Levetiracetam	29 (37.7 %)
Carbamazepine	18 (23.4 %)
Lamotrigine	12 (15.6 %)
Lacosamide	11 (14.3 %)
AED by MoA:	
Sodium channel blocker	55 (50.9 %)
SV2A binding	29 (26.8 %)
Multiple MoA	13 (12 %)
GABAergic tone enhancers	4 (3.7 %)
Other ion channel blockers	7 (6.4 %)
Median PER dose (mg/day) [IQR]	
Month 3	4 [4,4]
Month 6	4 [4,6]
Month 12	6 [4,8]
Reason for starting PER	
Failure to achieve seizure freedom	68 (88.3 %)
Intolerance to other AEDs	7 (9.1 %)
Poor adherence to other AEDs	2 (2.6 %)

3. Results

3.1. Patient characteristics and retention rate

Patient baseline characteristics are presented in Table 1 (n = 77). The median frequency of baseline seizures was 6 (2, 19). Failure to achieve seizure freedom with other AEDs (68 patients, 88.3 %) was the main reason for starting PER.

The rate of psychiatric comorbidity (determined from patients' medical records) was 32.5 % (25 patients), with the most frequent being anxiety (14 patients) and depression (13 patients).

Sodium channel blockers (47 patients, 61 %), followed by synaptic vesicle protein 2A modulators (29 patients, 37.7 %), were the most frequently associated AEDs.

The median dose of perampanel was 4 [4,4] mg/day at 3 months, 4 [4,6] mg/day at 6 months and 6 [4,8] mg/day at 12 months. Over 60 % of patients were maintained on 4 mg/day. Thirty out of 74 patients went

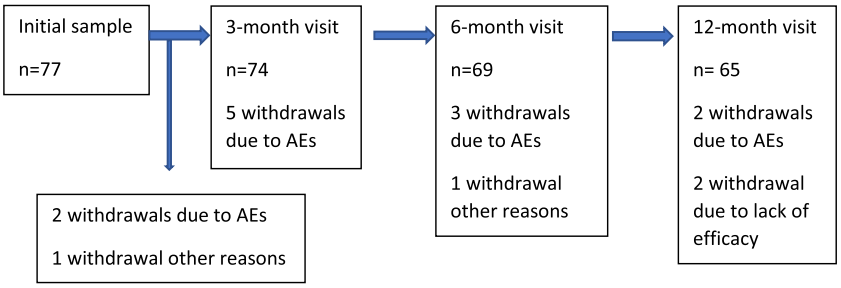

Fig. 1. Patient flow chart from baseline to 12 months.

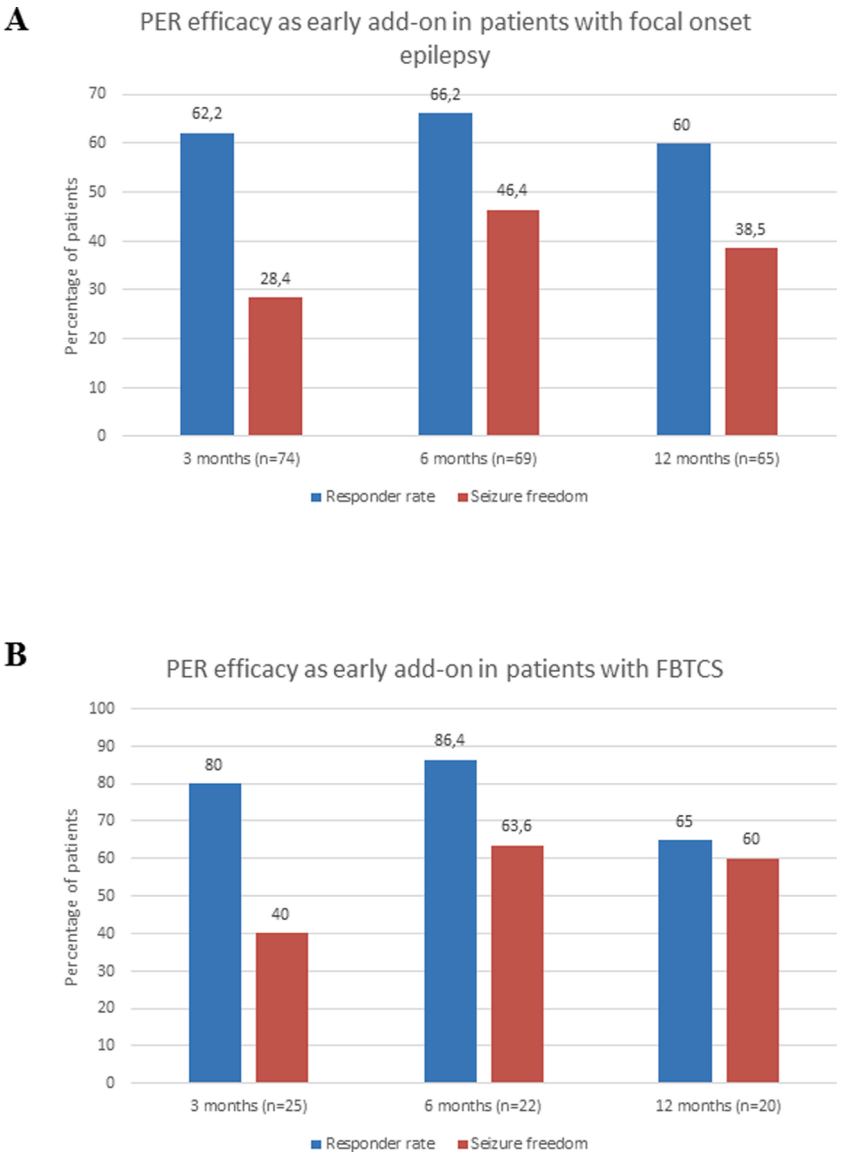

Fig. 2. Patients (%) with responder rate ≥50 % and seizure freedom, all FOS (A) and FBTCS (B).

from 2 mg to 4 mg in 1 week and stayed on that dose. Fourteen out of 74 patients went from 2 mg to 4 mg in 3 weeks. Data on the initial rate of increase of PER dose were missing for 3 patients. Retention rate was 89.6 % at 3 months (7 patients discontinued PER due to AEs and 1 due to other reasons), 84.4 % at 6 months (3 patients were withdrawn due to AEs and 1 due to other reasons) and 79.2 % after 12 months (2 patients were withdrawn due to AEs and 2 due to lack of efficacy). (Fig. 1). The probability of remaining on PER was 81.8 % after twelve months [**Supplementary** Fig. 1].

3.2. *Perampanel effectiveness*

The overall effectiveness of PER as an early add-on therapy in patients with FOS after 3, 6 and 12 months is shown in Fig. 2**A**. After 12 months of treatment 25/65 patients (38.5 %) were free of all seizures and 39/65 patients (60 %) experienced a ≥50 % reduction in seizure

Table 2
Drug-related adverse events.

Adverse events	Mild	Moderate	Severe	Total (n)	%	led to discontinuation (n)*
Somnolence	15	9	0	24	35,8	5
Irritability	11	5	1	17	25,4	8
Dizziness	6	4	1	11	16,4	3
Headache	2	1	0	3	4,5	1
Anguish	2	0	0	2	3,0	
Insomnia	2	0	0	2	3,0	
Anxiety	1	0	0	1	1,5	
Ataxia	1	0	0	1	1,5	1
Weight increase	0	1	0	1	1,5	
Confusion	0	1	0	1	1,5	1
Early morning awakening	1	0	0	1	1,5	
Aggressiveness	1	0	0	1	1,5	
Nightmares	1	0	0	1	1,5	1
Other	0	0	1	1	1,5	0
Total	43	21	3	67	100	

* PER was discontinued in 4 patients experiencing various AEs (3 each) and in 8 patients who experienced one AE.

frequency relative to baseline. The effect of PER on seizure freedom was statistically significant after 3, 6 and 12 months (McNemar test, $p < 0.05$; **Supplementary** Table 1).

As an early add-on, PER significantly reduces the median number of FBTCS at 3, 6 and 12 months (Wilcoxon test, $p < 0.05$; **Supplementary** Table 2). Sixty percent of patients experiencing FBTCS were seizure free after 12 months (12/20) and 65 % experienced a ≥50 % reduction in seizure frequency (13/20) (Fig. 2B).

The percentage of patients who experienced ≥50 % reduction in seizure frequency by month 12 was significantly higher when PER was given with one concomitant AED (26/36 patients; 72.2 %), compared to when PER was given with two concomitant AEDs (13/29 patients; 44.8 %) ($p < 0.05$; Chi-squared).

PER was the third AED prescribed to 15 out of 65 patients who were seizure free after 12 months.

3.3. Perampanel tolerability

Thirty-one patients (40.3 %) reported AEs, most of these (64.2 %) were mild. No deaths or sequelae due to treatment were documented. Sixty seven AEs associated with PER were recorded. The incidence and severity of these AEs is shown in Table 2.

The most frequent AEs were somnolence (24, 35.8 %), irritability (17, 25.4 %) and dizziness (11, 16.4 %). Twelve patients discontinued PER due to AEs after 12 months (15.6 %). Irritability was the main AE associated with treatment discontinuation (8 patients), followed by somnolence (5 patients) and dizziness (3 patients). The probability of experiencing AEs increases in patients over 65 years of age (13/77) and patients with concomitant AEDs with multiple mechanisms of action (valproic acid, topiramate) ($p < 0.05$; logistic regression analysis).

4. Discussion

In our experience, PER is an effective and safe early add-on therapy for patients with FOS. In our cohort of 77 patients, the retention rate after 12 months was 79.2 %. PER led to a ≥50 % reduction in seizure frequency in 60 % of patients and to seizure freedom in 38.5 % of patients after 12 months.

Previous studies in day-to-day clinical practice have shown lower retention and response rates after 12 months (Rohracher et al., 2018; Villanueva et al., 2016). Our high retention rate might be due to the low doses of PER employed (median 4 mg at 3 and 6 months and 6 mg at 12 months), even in patients taking concomitant enzyme-inducing AEDs (23.4 % on PER and carbamazepine), which can reduce the serum levels of PER (Patsalos et al., 2016). The doses used were established by the usual clinical practice of each doctor who participated in the study. Higher doses may have increased the drug's effectiveness but also its AEs.

Our study and others (Abril Jaramillo et al., 2020; Villanueva et al., 2018) confirm that the retention rate and seizure freedom can be significantly improved when PER is used as an early add-on.

We show that PER is particularly effective at reducing FBTCS, which are associated with significant risks to patients' safety and are one of the most significant risk factors for sudden unexpected death in epilepsy (SUDEP) (Hesdorffer et al., 2011). This is consistent with findings in Abril Jaramillo et al. (2020) and highlights the benefits of PER for patients with this type of seizures.

No significant differences in tolerability or effectiveness were observed with different concomitant AEDs, including LEV. The probability of experiencing AEs increased in patients taking AEDs with multiple mechanisms of action, but this should be interpreted cautiously due to the small sample size ($n = 12$). Older patients (> 65 years) also seemed to experience more AEs. This finding is not surprising, given that elderly patients are more sensitive to the side effects of AEDs (Acharya and Acharya, 2014).

The effectiveness of PER improved if administered with one concomitant AED rather than with two, which is also consistent with other studies (Abril Jaramillo et al., 2020; Kim et al., 2018; Villanueva et al., 2016). Although the probability of achieving seizure freedom seems to diminish with each subsequent AED tried (Chen et al., 2018), our study suggests that even as a third AED PER offers significant benefit.

There are a few limitations to this study, including the inherent limitations of the retrospective, observational study design, and the small sample size, which prevented statistical analisis between patient subgroups.

5. Conclusions

In our experience, PER is an effective and safe early add-on for patients with FOS, especially for those who experience FBTCS. The relatively low dose of PER required (4–6 mg/day) and the high retention rate after 12 months further reflect the drug's effectiveness and tolerability.

Declaration of Competing Interest

X. Rodríguez-Osorio has participated in advisory boards for UCB Pharma and ESTEVE and industry-sponsored symposia for Eisai, UCB Pharma, BIAL and ESTEVE.

E. Rubio-Nazábal has participated in industry-sponsored symposia for Eisai, BIAL, ESTEVE and UCB Pharma.

MD. Castro-Vilanova has participated in advisory boards for UCB and in industry-sponsored symposia for UCB, Bial, Eisai and Esteve.

A. Pato-Pato has participated in industry-sponsored symposia for Eisai.

J. Abella-Corral has participated in industry-sponsored symposia for Eisai, UCB, BIAL and ESTEVE.

A. Puy-Nuñez has participated in industry-sponsored symposia for UCB, Eisai, TEVA, Zambon, Lundbeck and Ferrer.

F.J. López-González has participated in advisory boards and industry-sponsored symposia for Eisai, UCB Pharma, BIAL and ESTEVE.

E. Corredera, A. López-Ferreira and T. Lema-Facal have nothing to declare.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eplepsyres.2021.106570.

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