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Comparative 12-month retention rate, effectiveness and tolerability of perampanel when used as a first add-on or a late add-on treatment in patients with focal epilepsies: The COM-PER study

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ABSTRACT

Objectives: To compare the 12-month retention rate, effectiveness and tolerability of perampanel (PER) as a first or late add-on treatment in adult patients with focal-onset seizures (FOS), including focal to bilateral tonic-clonic seizures (FBTCS).

Methods: This retrospective, observational, multicenter study was carried out in patients with FOS that received PER as a late add-on (n = 60), after failure of > 3 AEDs, and a group that received PER as a first add-on treatment (n = 21).

Results: At 12 months, the retention (90.5 % vs. 48.3 %; $p = 0.001$), seizure-freedom (71.4 % vs. 13.3 %; $p < 0.001$) and responder (85.7 % vs. 28.3 %; $p < 0.001$) rates were significantly higher in the first add-on group compared with the late add-on group. In patients with FBTCS, the 12-month retention rate did not differ significantly between the first and late add-on groups (93.8 % vs. 66.7 %); however, seizure-freedom (81.2 % vs. 27.8 %; $p = 0.002$) and responder rate response (93.8 % vs. 44.4 %; $p = 0.002$) were significantly higher in the first add-on group. There were no significant differences in tolerability between the two groups, including in patients with FBTCS. Adverse events were reported in 54.3 % of patients (44/81), most were mild or moderate, with dizziness being the most frequent one.

Conclusion: Overall, retention rate and effectiveness at 12 months were significantly higher in patients taking PER as a first add-on than as a late add-on, and the tolerability of PER did not differ significantly between groups. PER demonstrated high effectiveness in patients with FBTCS, even as a late add-on treatment.

1. Introduction

Perampanel (PER) is a first-in-class selective, non-competitive antagonist of the glutamate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor that has demonstrated broad-spectrum anticonvulsant activity [1,2]. In Europe, once-daily PER is indicated for the adjunctive treatment of focal-onset seizures (FOS), including focal to bilateral tonic-clonic seizures (FBTCS), and for primary generalized tonic-clonic seizures in patients over 12 years of age [3].

PER's tolerability and efficacy in reducing the frequency of both FOS and primary generalized tonic-clonic seizures has been shown in several randomized clinical trials and real-world studies [2]. Various extension studies and post-marketing studies have also assessed the retention rates of adjunctive PER [4–8], which indirectly reflects its long-term efficacy and tolerability [9].

Although the number of commercially available antiseizure drugs or medications (ASMs) has increased markedly over the past two decades [10], it is estimated that more than one third of patients with epilepsy still fail to achieve long-term remission. Refractory or drug resistant epilepsy — defined by the International League Against Epilepsy (ILAE) as "the failure of adequate trials of two tolerated, appropriately chosen

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Table 1
Baseline characteristics.

	Overall population		Patients with FBTCS at baseline	
	1 st add-on (n = 21)	Late add-on (n = 60)	1 st add-on (n = 16)	Late add-on (n = 18)
Median age, years	35 (20–59)	43 (30–55)	34 (19–61)	31 (27–43)
Gender male, n (%)	10 (47.6)	31 (51.7)	8 (50.0)	10 (55.6)
Epilepsy type, n (%)				
Frontal	5 (23.8)	18 (30)	5 (31.2)	8 (44.4)
Temporal	13 (61.9)	35 (58.3)	8 (50.0)	8 (44.4)
Parietal	3 (14.3)	2 (3.4)	3 (18.8)	–
Occipital	–	5 (8.3)	–	2 (11.1)
Aetiology, n (%)				
Perinatal complication	–	11 (18.3)	–	4 (22.2)
Cryptogenic	12 (57.1)	23 (38.3)	9 (56.2)	10 (55.6)
MTLS	2 (9.5)	13 (21.7)	1 (6.2)	1 (5.6)
CNS infection	–	1 (1.7)	–	1 (5.6)
MCD	1 (4.8)	5 (8.3)	1 (6.2)	1 (5.6)
Other	–	1 (1.7)	–	–
Trauma	1 (4.8)	1 (1.7)	1 (6.2)	1 (5.6)
Tumour	3 (14.3)	4 (6.7)	1 (6.2)	–
Vascular	3 (14.3)	1 (1.7)	3 (18.8)	–
Median age at onset (years)	21 (14–39)	16 (6–25)	30 (15–39)	13 (5–22)
Median time since diagnosis (years)	5.0 (2.5–9.5)	26 (16.0–36.0)	3.0 (2.0–7.0)	18.0 (15.0–28.5)
Median number of antiseizure drugs or medications at baseline	1 (1–1)	2 (2–3)	1 (1–1)	3 (2–3)
Median number of seizures at baseline (3 months prior to PER treatment)	4.0 (1.5–10.0)	7.0 (4.0–14.0)	3.0 (1.0–4.0)	4.5 (3.0–7.3)
Type of seizures, n (%)				
FAS	0 (0)	12 (20.3)	–	1 (5.6)
FIAS	6 (28.6)	40 (67.8)	1 (6.2)	8 (44.4)
FBTCS	16 (76.2)	18 (30.5)	16 (100)	18 (100)

FAS, focal awareness seizures; FBTCS, focal to bilateral tonic-clonic seizures; FIAS, focal impaired awareness seizures; IQR, interquartile range; MCD, malformations of cortical development; MTLS, mesial temporal lobe sclerosis.

and used anti-epileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" — remains prevalent [11,12]. One way to improve patients' seizure control and overcome pharmacoresistance is by combining ASMs with different mechanisms of action, but clear guidelines on when and how to combine ASMs is lacking, and current practice recommendations are largely empirical [13,14].

Some studies suggest that PER is more effective when administered as a first or early add-on, rather than later in the course of treatment [6,8,15–17]. To our knowledge only one study has directly compared the effects of PER as a first or late add-on treatment. Labate et al. [18] reported that in patients with mesial temporal lobe epilepsy PER was more effective and better tolerated as a first add-on than as a late-add on treatment. Our phase IV observational study (COM-PER) compares the effects of PER when used as first add-on or later adjunctive treatment in highly refractory patients with focal-onset seizures associated with different aetiologies, representing daily clinical practice.

2. Methods

2.1. Study design and participants

This was a retrospective, multicentre, observational study conducted in three hospitals in Portugal (Hospital Beatriz Ângelo; Centro Hospitalar Lisboa Ocidental; Hospital CUF Descobertas) involving patients with focal epilepsy receiving PER as first add-on (first add-on group) or later in the course of their treatment (late add-on group). Patients in the first add-on group were treated with one ASM as the initial monotherapy; the late add-on group consisted of highly refractory patients who failed to respond to ≥3 ASMs in the course of their treatment (mean of 5 previously failed ASMs, range 3–9; including patients with failed epilepsy surgery and/or vagus nerve stimulation).

All patients were recruited by the main investigator (NC). PER titration was based on the pharmacological profile of PER and clinical criteria. Both groups started with 2 mg of PER the first week. After that, and until the first 3 months of treatment, patients in the first add-on group were titrated up to 4 mg of PER; and in the late add-on group up to 6 mg of PER, with an intermediate dosage of 4 mg depending on concomitant ASMs (during 2 weeks if treated with enzyme-inducers ASMs, 4 weeks if not). During this period and over the following months the dosage of PER was adjusted according to clinical criteria.

Patients included were aged >12 years, had a clinical diagnosis of epilepsy with ≥1 focal seizure in the 3 months prior to treatment with PER, a complete and reliable seizure diary and ≥12 months follow-up. Patients enrolled in other studies, with incomplete clinical records or non-reliable data were excluded from the study.

Data were retrospectively extracted from clinical records at baseline and follow-up visits (3, 6, 9 and 12 months). Data obtained included sociodemographic characteristics, seizure types (according to the ILAE 2017 classification) [19], aetiology, age of epilepsy onset, previous ASMs, and number of ASMs and seizures in the 3 months prior to study entry (baseline). At follow-up, we evaluated the retention rate, seizure-freedom rate, responder rate, rate of non-response, PER dosage, as well as nature, severity and incidence of adverse events (AEs) considered related to PER.

Retention rate was defined as the proportion of patients remaining on PER at the time of assessment. Responder rate was defined as the proportion of patients who had ≥50 % reduction in seizure frequency in the last 3 months of evaluation compared with baseline. Seizure freedom rate was defined as the proportion of patients who were seizure free in the last 3 months of evaluation compared with baseline. The non-responder rate was defined as the proportion of patients that had a <50 % reduction in seizure frequency in the last 3 months of evaluation compared with baseline.

The study protocol was approved by Hospital Beatriz Ângelo Ethics Committee and followed the Declaration of Helsinki code of ethics. As an observational analysis of clinical practice, patient consent was not required as participation in this study did not affect their clinical care.

2.2. Endpoints

The primary endpoint was to assess the retention rate at 12 months in

Table 2
Retention rates and reasons for discontinuation of PER.

	Baseline		3 months		6 months		9 months		12 months	
	1 st add-on	Late add-on	1 st add-on	Late add-on	1 st add-on	Late add-on	1 st add-on	Late add-on	1 st add-on	Late add-on
Overall population										
Retention rate (n; %)	21 (100)	60 (100)	20 (95.2)	51 (85)	20 (95.2)	41 (68.3)	19 (90.5)	32 (53.3)	19 (90.5)	29 (48.3)
p value*	–		0.220		**0.014**		**0.002**		**0.001**	
OR (95 % CI)	–		3.53 (0.42–29.69)		**9.27 (0.16–74.24)**		**8.31 (1.78–38.88)**		**10.16 (2.17–47.49)**	
Discontinuation,										
Due to lack of efficacy (n, cumulative %)	–	–	0 (0 %)	7 (11.6 %)	0 (0 %)	6 (21.6 %)	0 (0 %)	6 (35 %)	0 (0 %)	3 (40 %)
Due to adverse events (n, cumulative %)	–	–	1 (4.7 %)	1 (1.6 %)	0 (4.7 %)	4 (8.3 %)	1 (9.5 %)	3 (13.3 %)	0 (9.5 %)	0 (13.3 %)
Other (n, cumulative %)			0 (0%)	1 (1.6 %)	0 (0%)	0 (1.6 %)	0 (0%)	0 (1.6 %)	0 (0%)	0 (1.6 %)
Total (cumulative n and %)			1 (4.7 %)	9 (15 %)	1 + 0 (4.7 %)	9 + 10 (31.7 %)	1 + 0+1 (9.5 %)	9 + 10 + 9 (46.7 %)	1 + 0+1 + 0 (9.5 %)	9 + 10 + 9 + 3 (51.7 %)
Patients with focal to bilateral tonic-clonic seizures										
Retention rate (n; %)	16 (100)	18 (100)	16 (100)	16 (88.9)	16 (100)	14 (77.8)	15 (93.7)	12 (66.7)	15 (93.8)	12 (66.7)
p value*	–		0.169		0.045		0.051		0.051	
OR (95 % CI)	–		5.0 (0.22–112.34)		10.24 (0.51–206.88)		7.50 (0.79–71.09)		7.50 (0.79–71.09)	
Discontinuation										
Lack of efficacy (n, cumulative %)	–	–	0 (0%)	1 (5.5 %)	0 (0%)	0 (5.5 %)	0 (0%)	2 (16.6 %)	0 (0%)	0 (16.6 %)
Adverse events (n, cumulative %)	–	–	0 (0%)	0 (0%)	0 (0%)	2 (11.1 %)	1 (6.25 %)	0 (11.1 %)	0 (6.25 %)	0 (11.1 %)
Other (n, cumulative %)	–	–	0 (0%)	1 (5.5 %)	0 (0%)	0 (5.5 %)	0 (0%)	0 (5.5 %)	0 (0%)	0 (5.5 %)
Total (cumulative n and %)	–	–	0 (0%)	2 (11.1 %)	0 + 0 (0%)	2 + 2 (22.2 %)	0 + 0+1 (6.25 %)	2 + 2+2 (33.3 %)	0 + 0+1 + 0 (6.25 %)	2 + 2+2 + 0 (33.3 %)

CI = confidence interval; OR = Odds ratio.
* chi-square.

patients treated with PER as first add-on and in patients treated with PER as late add-on. Secondary endpoints were to determine the effectiveness and tolerability of PER in both patient groups.

Effectiveness was determined from the responder and seizure-freedom rates for all seizures and FBTCS at 3, 6, 9 and 12 months. Tolerability was assessed by recording the incidence of AEs during 12 months of treatment and the proportion of patients who discontinued PER treatment due to an AE during the 12 months observation period.

2.3. Statistical analysis

Descriptive and frequency statistics were obtained for the variables studied. The statistical significance of intergroup differences was assessed by Pearson's chi-square test for categorical variables. Cox regression was used to examine associations between treatment discontinuation and gender, age, epilepsy type, and treatment type. The effect size of dose on treatment discontinuation was determined by calculating Cohen's d-statistic (d = 0.2 is considered a 'small' effect size, 0.5 a 'medium' effect size and 0.8 a 'large' effect size) [20]. IBM SPSS v.24 (IBM, Armonk) software was used for statistical analyzes.

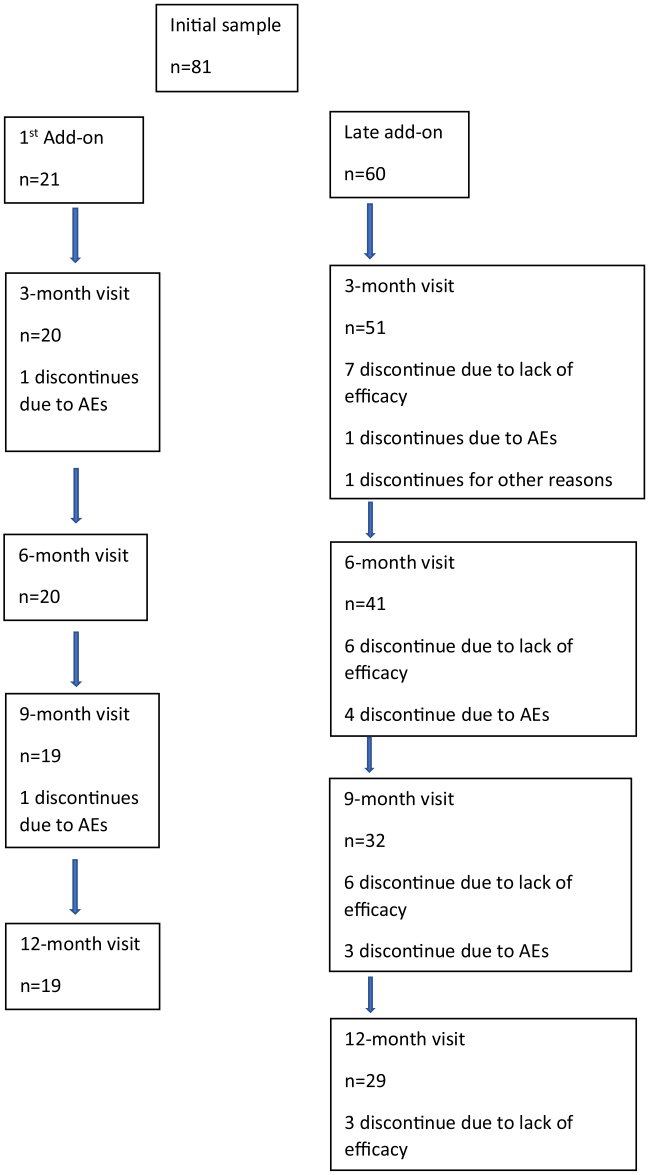

Fig. 1. Patient flow chart from baseline to 12 months.

3. Results

3.1. Patient characteristics

Eighty-one patients were included in the primary analyses; 21 were receiving PER as first add-on therapy (median age 35 years, IQR 20-59) and 60 highly refractory patients (mean of five previously failed ASMs, range 3-9) were receiving PER as a late add-on therapy (median age 43 years, IQR 30-55). The demographics and clinical characteristics of the patients are summarised in Table 1. The median age at the onset of epilepsy in the first add-on group was 21 years (IQR 14-39) and the median time since diagnosis was 5 years (IQR 2.5-9.5), while the median age at the onset of epilepsy in the late adjunctive group was 16 years (IQR 6-25) and the median time since diagnosis was 26 years (IQR 16-36). At the time of PER initiation, patients in the first add-on group were experiencing a median of four seizures every 3 months (IQR 1.5-10) and those in the late add-on group patients were experiencing a median of seven (IQR 4-14) seizures every 3 months. Overall, 16 patients (76 %) in the first add-on group and 18 (31 %) in the late add-on group were experiencing FBTCS.

3.2. Retention rates

At 12 months, the retention rate of patients with FOS taking PER was significantly higher in the first add-on group than in the late add-on group (90.5 % vs. 48.3 %; $p = 0.001$), with significant between-group differences seen from 6 months onwards (Table 2). Over the 12 month follow-up period, PER was discontinued in two patients in the first add-on group (9.5 %, both due to AEs, no patient discontinued PER due to lack of efficacy) and in 31 patients in the late add-on group (51.7 %), mostly due to lack of efficacy (Table 2; Fig. 1).

In the subgroup of patients with FBTCS, although the retention rate during the observational period was superior in the first add-on group, it did not differ significantly between patients in the first and late add-on groups at 12 months (93.8 % vs. 66.7 %), and no significant between-group differences were seen at any time during follow-up (Table 2). In this subgroup, none of the patients in the first add-on group and only three (16.6 %) in the late add-on group discontinued PER due to lack of efficacy (Table 2).

A multivariate cox regression analysis showed that treatment type was the only variable significantly associated with the time to treatment discontinuation, both in the overall population ($p = 0.004$) and in patients with FBTCS at baseline ($p = 0.044$) (Table 3), demonstrating that patients taking PER as a late add-on were more likely to discontinue treatment than those taking PER as a first add-on.

3.3. Effectiveness assessments

In the overall population, at 12 months, patients receiving PER as first add-on therapy had higher responder (85.7 % vs. 28.3 %; $p < 0.001$) and seizure-freedom (71.4 % vs. 13.3 %; $p < 0.001$) rates than patients receiving the drug as a late add-on therapy (Table 4). During the follow-up period, the first add-group had significantly higher response and seizure freedom rates than the late add-on group, only with the exception of response rates at 6 months.

In patients with FBTCS, the first add-on group had a significantly higher responder rate (93.8 % vs. 44.4 %; $p = 0.002$) and seizure-freedom rate (81.2 % vs. 27.8 %; $p = 0.002$) than the late add-on group at 12 months, with significant between group differences in seizure freedom observed at 3 months, and in response rate at 9 months (Table 4).

The proportion of patients with <50 % reduction in seizure frequency was at least two-fold higher in the first add-on group than in the late add-on group, both in the overall population and in patients with FBTCS (Table 4).

Table 3
Cox regression analysis of time to discontinuation of treatment.

	Exp(B)	95 %CI	p-value
Overall population			
Gender, female	1.239	0.608–2.524	0.555
Age (1-year increments)	1.000	0.972–1.029	0.983
Epilepsy type			
Frontal	Ref	Ref	–
Temporal	3.339	0.222–50.212	0.383
Parietal	4.188	0.280–67.714	0.300
Occipital	15.077	0.677–335.597	0.087
Time since diagnosis	0.994	0.965–1.024	0.684
Number of previous seizures	1.004	0.991–1.017	0.543
Treatment type	10.377	2.083–51.712	**0.004**
Patients with focal to bilateral tonic-clonic seizures			
Gender, female	1.239	0.608–2.524	0.555
Age (1-year increments)	0.833	0.168–4.124	0.823
Epilepsy type			
Frontal	Ref	Ref	–
Temporal	2439.9	$0.000–10^{151}$	0.964
Parietal	1865.9	$0.000–10^{151}$	0.965
Occipital	0.424	$0.000–10^{195}$	0.997
Time since diagnosis	0.917	0.814–1.034	0.156
Number of previous seizures	0.986	0.871–1.116	0.826
Treatment type	14.726	1.075–201.735	**0.044**

3.4. Safety and tolerability

PER was generally well tolerated as first add-on or late add-on therapy in patients with focal-onset seizures, including FBTCS. Treatment emergent AEs (TEAEs) occurred in 54.3 % of patients (44/81), 38.1 % in the first add-on group (8/21) and 60 % in the late add-on group (36/60) at 12 months. Most patients had mild (19/44, 43.2 %) or moderate (17/44, 39.6 %) AEs which did not lead to PER discontinuation, and were controlled with dosage adjustments. The most common AE was dizziness (27/44, 61.4 %) followed by irritability (13/44, 29.5 %). Only 13.6 % (11/81) of patients discontinued PER due to TEAEs (Table 5). There were no significant differences in the percentage of patients with TEAEs or in the severity of TEAEs between the first add-on group and the late add-on group. Furthermore, there were no significant differences in the percentage of patients discontinuing treatment because of TEAEs between the two groups at 12 months (Table 5). Similarly, no differences in TEAEs were found between the first and late add-on FBTCS groups, indicating that PER tolerability is not linked to seizure type.

In the overall population, there was no significant difference in the median dose between patients continuing PER and those discontinuing treatment because of AEs at 3 months [median (IQR) 6 (6–6) vs. 5 (4–5) mg], 6 months [6 (4–8) vs. 8 (6.5–8) mg] or 9 months [6 (4–8) vs. 8 (6.5–9.5) mg]. No patient discontinued treatment because of AEs at 12 months.

4. Discussion

Our observational, phase IV study shows that after 6, 9 and 12 months, the retention and response rates were significantly higher in patients with FOS receiving PER as a first add-on than in those receiving the drug as a late add-on therapy. There were no differences in tolerability between the two groups at any point during the study. Additionally, PER demonstrated high effectiveness in patients with FBTCS, including refractory patients, suggesting that PER could benefit refractory patients experiencing this type of seizures, which are a strong risk factor for SUDEP [21,22].

To our knowledge only one other study has directly compared the effects of PER at different stages of epilepsy treatment [18]. In that study, which included 37 patients with mesial temporal lobe epilepsy, both the responder and seizure freedom rates were higher in patients

Table 4
Effectiveness outcomes.

	3 months		6 months		9 months		12 months	
	1 st add-on	Late add-on	1 st add-on	Late add-on	1 st add-on	Late add-on	1 st add-on	Late add-on
Overall population								
Responder rate (seizure freedom + >50 % improvement) n (%)	19 (90.5)	35 (58.3)	15 (71.4)	28 (46.7)	18 (85.7)	19 (31.7)	18 (85.7)	17 (28.3)
p value	**0.006**		0.058		**<0.001**		**<0.001**	
OR (95 % CI)	6.99 (1.49–32.77)		2.77 (0.94-8.12)		12.63 (3.31–48.18)		14.83 (3.86–56.95)	
Seizure-freedom rate n (%)	11 (52.4)	15 (25)	12 (57.1)	13 (21.7)	14 (66.7)	9 (15)	15 (71.4)	8 (13.3)
p value	**0.015**		**0.003**		**<0.001**		**<0.001**	
OR (95 % CI)	3.54 (1.24–10.06)		4.72 (1.63–13.63)		11.11 (3.51–35.14)		15.94 (4.78–53.18)	
Patients with <50 % improvement n (%)	2 (9.5)	25 (42.4)	6 (28.6)	31 (52.5)	3 (14.3)	40 (67.8)	3 (14.3)	42 (71.2)
Patients with focal to bilateral tonic-clonic seizures								
Responder rate (seizure freedom + >50 % improvement) n (%)	15 (93.8)	14 (77.8)	13 (81.2)	10 (55.6)	16 (100)	8 (44.4)	15 (93.8)	8 (44.4)
p value	0.100		0.110		**<0.001**		**0.002**	
OR (95 % CI)	5.77 (0.59–55.95)		3.47 (0.73–16.53)		40.76 (2.12–782.95)		18.75 (2.02–173.94)	
Seizure freedom rate n (%)	10 (62.5)	10 (55.5)	11 (68.8)	6 (33.3)	12 (75.0)	6 (33.3)	13 (81.2)	5 (27.8)
p value	0.464		**0.039**		**0.015**		**0.002**	
OR (95 % CI)	1.67 (0.42–6.56)		4.04 (1.04–18.60)		6.00 (1.34–26.81)		11.27 (2.22–57.20)	
Patients with <50 % improvement n (%)	1 (6.2)	5 (27.8)	3 (18.8)	8 (44.4)	0 (0.0)	10 (55.6)	1 (6.2)	10 (55.6)

Table 5
Treatment Emergent Adverse Events (TEAE).

	3 months		6 months		9 months		12 months	
	1 st add-on	Late add-on	1 st add-on	Late add-on	1 st add-on	Late add-on	1 st add-on	Late add-on
Any TEAE (n at each time evaluation)	5/21	10/60	1/20	14/51	2/20	10/41	0/19	2/32
Chi-square	0.468		0.037		0.184		0.266	
TEAE intensity (n, cumulative)							**Total n and percentage**	
Mild	2	6	3	12	4	14	4/21 (19 %)	15/60 (25 %)
Moderate	2	4	2	8	3	13	3/21 (14.3 %)	14/60 (23.3 %)
Severe	1	0	1	4	1	7	1/21 (4.4 %)	7/60 (11.7 %)
Most common TEAEs (n, cumulative)								
Dizziness	4	7	5	15	5	20	5/21 (23.8 %)	22/60 (36.7 %)
Somnolence	0	0	0	2	0	3	0/21	3/60 (5%)
Irritability	1	3	1	7	3	10	3/21 (14.3 %)	10/60 (16.7 %)
Instability	0	0	0	0	0	1	0/21	1/60 (1.7 %)
TEAE leading to PER discontinuation (n, cumulative)								
Dizziness	–	1	–	2	–	4	0/21	4/60 (6.7 %)
Somnolence	–	–	–	1	–	1	0/21	1/60 (1.7 %)
Irritability	1	–	–	3	2	3	2/21 (9.5 %)	3/60 (5%)
Instability	–	–	–	–	–	1	0/21	1/60 (1.7 %)

receiving PER as a first add-on than as a late add-on due to inefficacy of ≥2 ASMs. Our study in more refractory patients (who have failed to respond to ≥3 ASMs) with FOS associated with different aetiologies is consistent with Labate et al. [18].

Our 12-month retention rate with PER as a first add-on is slightly higher than that reported with comparable doses and titration scheme as an early add-on (90.5 % vs. 80.5 %) [8] in patients with FOS. It is also higher than that reported in Korean patients with focal or primary generalised seizures receiving PER as a first add-on (64.7 %) [5]. These differences may be due to differences in the study populations, namely the type of seizures and the position in which PER was used in the treatment algorithm of FOS (first vs early add-on).

Regarding patients in which PER was used as a late add-on, our 12-month retention rate (48.3 %) is similar to that reported in a large, multicentre study by Rohracher [6] (48 %), which included 2396 patients, 95 % having FOS treated with a median of 6 other ASMs. Other studies have reported higher 12-month retention rates with PER in refractory patients with FOS, ranging from 60.6 %–71.1 % [15,23,24], these differences could be due to different levels of patient refractoriness or to methodological approaches (titration schemes, data analysis).

Although a higher retention rate and better response rates were observed in patients taking PER as a first add-on compared to a late add-on, there were no significant differences in tolerability between the groups highlighting the safety of PER irrespective of treatment stage.

The response rate we observed after 12 months in patients taking PER as a first add-on (85.7 %) and seizure freedom rate (71.4 %) are higher than those reported with PER as an early add on in the PERADON study (68.1 % and 26.5 %, respectively) [8], but our findings are consistent with their findings that PER is more effective as a first than as a second adjunctive therapy.

The response rate in patients taking PER for 12 months as a late add-on (28.3 %) is in line with previous studies [6,23,24], but our seizure freedom rate (13.3 %) was higher than in those studies, which can be due to the high percentage of patients with FBTCS included in our study (34/81, 42 %). When we assessed the retention rates and effectiveness of PER as first or late add-on therapy among patients with FBTCS at baseline, we found that the response and seizure freedom rates in this subgroup were also significantly higher in patients receiving PER as first add-on therapy than in those receiving the drug as late add-on therapy. However, the retention rates did not differ significantly between the two groups. Moreover, better response and seizure freedom rates were observed in patients with FBTCS compared to the overall population, even when PER is administered as a late add on (response rate 44.4 % and seizure freedom 27.8 %), suggesting that PER is particularly effective in these type of seizures and could also benefit highly refractory patients with FBTCS.

Similar proportions of first and late add-on group patients discontinued treatment because of AEs, both in the overall population (9.5 % and 13.3 %) and in patients with FBTCS (6.25 % and 11.1 %). These percentages are similar to those reported in other studies [8,23,24]. Most AEs were mild to moderate and we did not see any previously unknown adverse events. A strength of this study is the 'real-world' setting representative of day-to-day clinical practice, with different aetiologies included in the first and late add-on groups. In addition, one investigator recruited all patients, thereby reducing variability in the method of collection and creation of clinical records, and set the titration schemes.

This study has several limitations, including the small sample size of the study population (particularly the first add-on group), the retrospective, observational study design, and the lack of a control group and blinding. Because patients with incomplete clinical records or non-reliable data were excluded, we may have missed patients who did not respond or discontinued treatment over the course of 1 year. It is also worth noting that patients who took PER as a late add-on had more hippocampal sclerosis, malformation of cortical development (MCD) and perinatal complications (aetiologies associated with difficult to

control epilepsies [25]) than patients in which PER was used as a first add-on (Table 1). In addition, patients taking PER as a first add-on, had more cryptogenic and vascular focal epilepsies, aetiologies that are generally easier to control [25]. Nevertheless, this type of study provides an important insight into the real-world use of PER in patients with focal epilepsies and its potential benefit to patients with FBTCS.

5. Conclusion

PER was effective and well tolerated both as first add-on therapy, as well as late adjunctive treatment in patients with focal epilepsy. While retention, response and seizure-freedom rates at 12 months were significantly higher in the first add-on group than in the late add-on group, the tolerability of PER in the two groups did not differ significantly throughout follow-up. Although limited by the small sample size, the retention rate and effectiveness of PER was particularly high in patients with FBTCS, even when administered as a late add-on.

Author contributions

Nuno Canas was responsible for the concept of this study and for the identification of all patients included; Catarina Félix, Vanessa Silva and Ana Arraiolos contributed to the data collection and analysis; Fernando Fernandez-Llimos was responsible for the statistical analysis of the presented data.

Declaration of Competing Interest

The authors have no conflicts of interest or financial disclosures relevant for his study.

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