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ABSTRACT

Purpose: To investigate the efficacy and tolerability of perampanel (PER) when administered as a first add-on therapy to patients with focal epilepsy or idiopathic generalized epilepsy (IGE) taking one other antiseizure drug (ASD).

Methods: This multicentre, retrospective, one-year observational study collected data from patients (≥12 years) who initiated treatment with PER as first add-on therapy. Patients had to be experiencing inadequate seizure control on ASD monotherapy and tried ≤3 ASD monotherapies before initiating PER. Multivariate logistic regression analyses were performed, adjusted for the number and type of previous seizures, duration and aetiology of epilepsy.

Results: Of the 149 patients included in the study (mean age 41 years; 54.4 % male), 118 (79.2 %) were still receiving PER as first add-on treatment after 12 months. Mean PER dose was 6.2 mg/day. At 12 months, 45.6 % were seizure-free and 84.6 % responders. A significant difference in seizure freedom rate was found between

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; ASD, antiseizure drug; BRV, brivaracetam; BZD, benzodiazepines; CBZ, carbamazepine; ESL, eslicarbazepine acetate; GBP, gabapentin; IGE, idiopathic generalized epilepsy; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PER, perampanel; PGB, pregabalin; PHT, phenytoin; SCB, sodium-channel blockers; TPM, topiramate; VPA, valproic acid; ZNS, zonisamide.

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patients with IGE and patients with focal epilepsy, but not in responders. Reduced seizure control was observed when PER was administered with strong enzyme-inducing ASDs; conversely, increased seizure control was seen when the same dose of PER was combined with enzyme-inhibiting ASDs. The most frequent adverse events were dizziness (15.4 %), irritability (14.1 %) and drowsiness (14.1 %); no differences in tolerance were observed among different combinations.

Conclusion: PER demonstrated a good efficacy and safety profile when used as a first add-on therapy in patients who did not respond to monotherapy. PER dose adjustments may optimize seizure control when combined with strong enzyme-inducing or enzyme-inhibiting ASDs.

1. Introduction

Anti-seizure drugs (ASDs) are the mainstay of treatment for most patients with epilepsy. [1] The number of commercially available ASDs has increased markedly over the past two decades [2]; however, older ASDs are still frequently prescribed. Furthermore, despite the increasing choice in available agents, it is estimated that more than one third of patients with epilepsy still fail to achieve long-term remission [3,4]. One potential way of improving patients' seizure control is to optimize combinations of ASDs with different mechanisms of action [4].

Perampanel (PER) is approved in Europe for once-daily adjunctive therapy of patients (≥12 years old) with focal-onset seizures including focal to bilateral tonic-clonic seizures, [5,6] as well as for generalized tonic-clonic seizures in patients ≥12years with idiopathic generalized epilepsy (IGE) [5]. PER is a first-in-class selective non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor antagonist [7,8]. AMPA receptors are activated by the neurotransmitter glutamate, which is thought to play an important role in inducing seizures and AMPA receptors are crucial in the generation and spread of epileptic activity [9].

Preclinical studies have demonstrated that PER has broad-spectrum anticonvulsant activity, [10] and clinical studies have shown its efficacy and tolerability in patients with refractory epilepsy in adult and paediatric populations [11–15].The effect of PER on AMPA receptors has been demonstrated to be useful in generalized tonic-clonic and focal to bilateral tonic-clonic seizures, and myoclonic seizures in refractory patients [16–20]. There is also preliminary evidence that PER is more effective when used early in the treatment pathway [21]. However, little is known about the potential synergistic effects of PER with other ASDs.

A retrospective study suggested that patients taking fewer prior ASDs had a more favourable clinical response to PER and that, similar to other ASDs, PER has better results in less refractory cases. [21] Similarly, in a pooled observational analysis of data from >2000 patients from 45 European centres, a higher number of previous ASDs was associated with a lower seizure free rate in patients receiving PER. [22]. Another study investigating the efficacy and tolerability of PER as a first add-on therapy in controlling secondarily generalized seizures in patients with focal epilepsy showed that PER was as effective as levetiracetam (LEV) as first add-on therapy, with a better tolerability profile [23].

Both randomized controlled studies and real-life studies have shown that PER has a good tolerability profile, with the most common adverse events being dizziness/vertigo, behavioural reactions, including irritability, and sedative effects. [21,22,24] Adverse events are more common with higher doses, but there is no specific information regarding tolerability as first add-on.

The aim of this study was to evaluate the efficacy and tolerability of PER when administered as a first add-on therapy to adolescents and adults with epilepsy in everyday clinical practice. A second aim of our study was to determine the preferred combination of PER and another ASD in terms of efficacy and tolerability.

2. Methods

2.1. Study design and participants

This retrospective, one-year observational study involved epilepsy specialists from 22 hospitals across Spain. Data from male and female patients (≥12 years of age) diagnosed with focal epilepsy or IGE who initiated treatment with PER as a first-add on therapy between September 2015 to January 2017 were collected. Diagnosis of epilepsy was made on clinical grounds, following the principles of the 2017 International League Against Epilepsy (ILAE) classification, [25] and supported by electroencephalogram (EEG) data. Patients were included if they were experiencing inadequate seizure control on ASD monotherapy (≥ 1 seizure per month during the 6 months previous to the inclusion) and had tried ≤3 ASD monotherapies before initiating PER as a first add-on. Patients were excluded if had an unclear diagnosis of epilepsy, were pregnant or breastfeeding, if the adherence to treatment was not correct or if they had an inadequate case history. All possible candidates to be included were reviewed systematically by different authors to ensure they met the inclusion criteria.

The study was conducted in accordance with the protocol and the ethical principles outlined in the Declaration of Helsinki. The study was classed as a post-approval study by the Spanish Agency of Medicine and Health Products (AEMPS) and was approved by the Ethics Committee of Bellvitge University Hospital (EPA029/18). 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. Outcomes

Data were collected from patients' clinical records and kept in a single electronic database to retrospectively assess the efficacy and tolerability of ASDs. Data were extracted from patient charts at baseline, and at 3, 6 and 12 months after initiating PER treatment.

Demographic and clinical characteristics included gender, age, weight, age at onset of epilepsy, the number of seizures per month before inclusion, seizure type, aetiology, presence or absence of psychiatric comorbidity, as well as treatment parameters, such as the main reason for adding PER as first add-on therapy, the dose of PER administered at 3, 6 and 12 months, titration scheme, and any concomitant ASDs.

The primary efficacy variables were the proportion of seizure-free patients at 12 months at least during the last 6 months, and the proportion of patients achieving ≥50 % reduction in seizure frequency at 12 months at least during the last 6 months (responders). Analysis was by intention to treat. Seizures were classified according to the ILAE 2017 operational classification of seizure types. [26]

The tolerability of PER was assessed by recording the incidence of adverse events (AEs) during 12 months of treatment, the type of AE, their evolution through the follow-up and the proportion of patients who discontinued PER treatment due to an AE.

Exploratory analyses examined efficacy and tolerability outcomes in the following patient subgroups: by type of seizure and by the mechanism of action of concomitant ASDs. ASDs were classified as either sodium channel blockers (SCB) (phenytoin (PHT), carbamazepine (CBZ), oxcarbazepine (OXC), eslicarbazepine acetate (ESL), lamotrigine (LTG),

lacosamide (LCM)), [27] synaptic vesicle protein 2A modulators (LEV, brivaracetam (BRV)) [28,29], gamma-aminobutyric acid analogues (phenobarbital (PB), benzodiazepines (BZD)) [30] or ASDs with multiple mechanisms of action (gabapentin (GBP), pregabalin (PGB), valproic acid (VPA), topiramate (TPM), zonisamide (ZNS)) [31–34]. Another analysis was conducted to examine the effects of ASDs according to their ability to stimulate enzymes, with CBZ, PB, PHT classified as "strong" enzyme-inducing ASDs, ESL, OXC and TPM classified as "moderate" enzyme-inducing ASDs, VPA classified as an enzyme inhibitor, and the remaining ASDs classified as non-inducing ASDs [35–37].

2.3. Statistical analysis

All analyses were conducted in the 'included population', defined as all patients who met the inclusion criteria. All variables were analysed by summary statistical methods. For continuous/quantitative variables, descriptive statistics including the arithmetic mean, and standard deviation (SD), minimum and maximum were calculated. For categorical/qualitative variables, absolute frequencies and percentages were generated.

For the efficacy analyses, differences between patient groups were assessed using the Kruskal–Wallis test or the Mann–Whitney *U* test for quantitative variables and Chi-square tests for qualitative variables. Changes over time were analysed using the Friedman or the Wilcoxon test for quantitative variables and the Cochran or the McNemar test for binary variables. A multivariate logistic regression analysis, adjusted for the type, duration, and aetiology of epilepsy, was carried out to determine the odds ratio (OR) of seizure freedom with all drug combinations. All analyses were conducted with a predefined significance level of 0.05

The statistical analysis was performed using the software package SPSS version 19.0 (IBM Corporation, Armonk, NY, USA).

3. Results

Of the 149 patients included in the study (mean age 41 years; 54.4 % male), 118 (79.2 %) were still receiving PER treatment after 12 months (Fig. 1). The most common reasons for treatment discontinuation were AEs (n = 15, 10.1 %), lack of efficacy (n = 11, 7.4 %), and both AEs and lack of efficacy (n = 5, 3.4 %).

The majority of patients included in the study had focal epilepsy (77.9 %), and 22.1 % were diagnosed with IGE. In focal epilepsy, the most frequent seizure reported was focal impaired awareness (45 %); and in IGE, 21 out of 32 patients showed generalized tonic-clonic seizures, 11 myoclonic seizures, 10 absences and 1 tonic seizures. The aetiology of epilepsy was unknown in 49.7 % of patients, other causes included: vascular (12.1 %), trauma (6.7 %), cavernoma (5.4 %), malformation of cortical development (4 %), tumour (3 %), temporal mesial sclerosis (3 %), perinatal hypoxia (0.7 %) and other (14.8 %). Psychiatric comorbidities were present in 22.8 % of patients, with anxiety (12.1 %) being the most frequent (Table 1). Most patients (85.9 %) initiated PER after failure of one previous ASD monotherapy; the most commonly used concomitant ASDs were LEV (37.8 %), LTG (16.2 %), and VPA (14.9 %; Table 1). For 90.9 % of patients, the main reason for

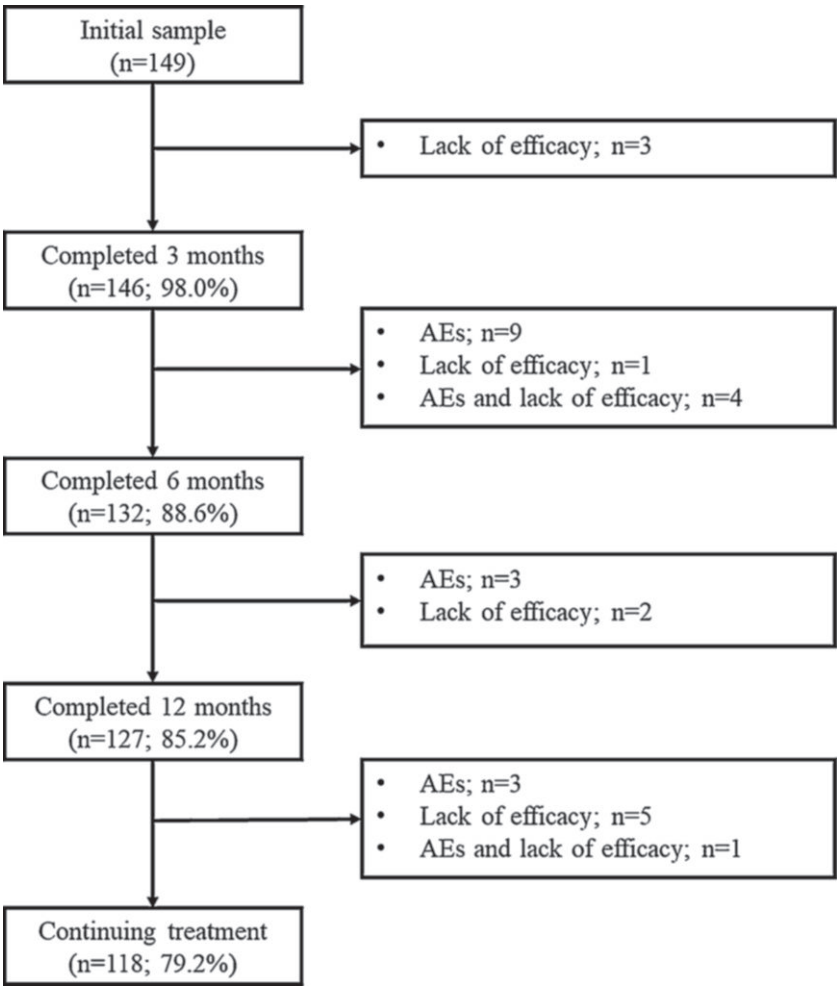

Fig. 1. Patient flow. AEs, adverse events.

Table 1
Baseline characteristics.

Characteristic	N = 149
Mean (range) age, years	41 (12–84)
Male, n (%)	81 (54.4)
Mean ± SD time since diagnosis of epilepsy, years	9.6 ± 11.4
Mean (range) age at epilepsy onset, years	31.4 (0–83)
Median number of seizures/month before inclusion (IQR)	1.7 (1–2.9)
Bodyweight, n (%)	
<45 kg	2 (1.3)
45–90 kg	139 (93.3)
>90 kg	8 (5.4)
Type of epilepsy, n (%)**	
Generalized	32 (22.1)
Generalized tonic-clonic seizures*	21 (14.1)
Myoclonic seizures*	11 (7.4)
Absence seizures*	10 (6.7)
Tonic seizures*	1 (0.7)
Focal	113 (77.9)
Focal aware seizures*	45 (30.2)
Focal impaired awareness seizures*	67 (45.0)
Focal to bilateral tonic-clonic seizures*	53 (35.6)
Aetiology, n (%)	
Vascular	18 (12.1)
Trauma	10 (6.7)
Cavernoma	8 (5.4)
Malformation of cortical development	6 (4.0)
Tumour	5 (3.4)
Temporal mesial sclerosis	5 (3.4)
Perinatal hypoxia	1 (0.7)
Other	22 (14.8)
Unknown	74 (49.7)
Number of previous ASDs, n (%)	
1	128 (85.9)
2	18 (12.1)
3	3 (2)
Psychiatric comorbidities, n (%)	34 (22.8)
Anxiety	18 (12.1)
Depression	10 (6.7)
Hyperactivity	5 (3.4)
Personality disorder	3 (2.0)
Autism	2 (1.3)
Psychosis	1 (0.7)
Concomitant ASDs, n (%)	
Levetiracetam	56 (37.8)
Lamotrigine	24 (16.2)
Valproic acid	22 (14.9)
Eslicarbazepine acetate	10 (6.8)
Carbamazepine	9 (6.1)
Oxcarbazepine	8 (5.4)
Lacosamide	7 (4.7)
Zonisamide	5 (3.4)
Topiramate	3 (2.0)
Brivaracetam	1 (0.7)
Phenytoin	1 (0.7)
Phenobarbital	1 (0.7)
Gabapentin	1 (0.7)

*Patients could be classified as belonging to more than one category for type of crisis.
ASDs, anti-seizure drugs; SD, standard deviation.
** Four patients had unclassifiable epilepsy.

initiating PER was poor seizure control and the median number of seizures per month before inclusion was 1.7 (1–2.9). The concomitant ASDs doses were in the standard range of efficacy.

The mean dose of PER among patients receiving PER at 12 months was 6.2 mg/day (median 6 mg/day) and no differences in the PER dose were seen among patients with focal epilepsy versus IGE or between patients taking different concomitant ASDs with different mechanisms of action. The doses of PER significantly increased over the observation period ($p < 0.001$), with the most frequent titration scheme being 2 mg every 4 weeks (39.7 %) or 2 mg every 2 weeks (36.2 %).

3.1. Efficacy

After 12 months of PER therapy, 45.6 % of the 149 included patients with focal epilepsy or IGE were free of all seizures and 84.6 % were considered responders. 62.5 % of patients with IGE were seizure free compared with 40.7 % of patients with focal epilepsy ($p = 0.029$). No significant differences in responder rate were found between patients with IGE and patients with focal epilepsy after 12 months of PER treatment. After 12 months of therapy, 93.8 % of patients with IGE were considered responders versus 82.3 % of patients with focal epilepsy ($p = 0.111$) (Fig. 2).

At 12 months, PER treatment reduced the number of focal seizures and generalized seizures, with a 64.7 % reduction from baseline in the median number of focal seizures per month and a 75.0 % reduction from baseline in the median number of generalized seizures per month (both $p < 0.01$). Furthermore, at 3 and 6 months, there was also a significant reduction from baseline in the median number of focal or generalized seizures per month (all $p < 0.001$) with PER treatment.

When analysed by focal seizure type, a similar trend with PER treatment was observed, with the number of focal aware seizures, focal impaired awareness seizures and focal to bilateral tonic-clonic seizures declining during the observation period (all $p < 0.001$ vs baseline). At 12 months, the number of focal aware seizures, focal impaired awareness seizures and focal to bilateral tonic-clonic seizures were reduced by 70.7 %, 65.4 % and 75.0 %, respectively (all $p < 0.01$).

When analysed by generalized seizure type, the number of tonic-clonic seizures, myoclonic seizures and absence seizures also declined during the observation period (all $p \leq 0.001$ vs baseline). Furthermore, the number of generalized tonic-clonic seizures, myoclonic seizures and absence seizures per month were reduced by 87.5 %, 90.9 % and 87.5 %, respectively, at 12 months (all $p < 0.01$).

3.2. Tolerability

PER was generally well tolerated, with 48.3 % of patients experiencing an AE over the 12-month observation period. Most of the AEs reported were mild to moderate in intensity, and the most common AEs were dizziness (15.4 % of patients), irritability (14.1 %), drowsiness (14.1 %), anxiety (6.7 %), and fatigue (6.0 %; Table 2).

Most AEs were experienced in the first 3 months of treatment, with 35.6 % of patients reporting an AE during this period compared with 21.2 % reporting an AE between 3 and 6 months of treatment and 15.7 % of patients between 6 and 12 months of treatment. Between 33.0 % and 43.0 % of patients who reported dizziness, drowsiness, and fatigue with PER treatment found that these AEs disappeared after 3 months (Supplementary Table 1).

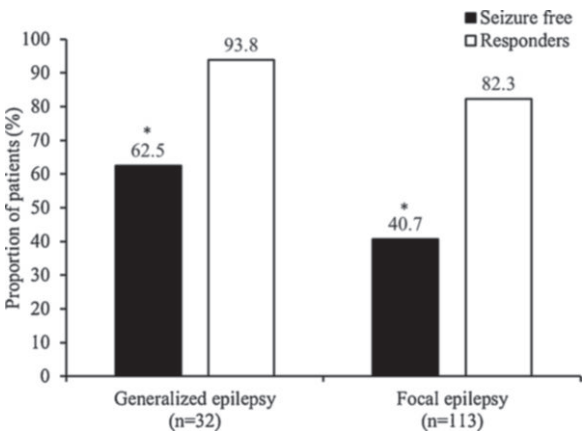

Fig. 2. Overall efficacy (all seizure types) of perampanel as a first add-on therapy at 12 months in patients (n = 149) with generalized and focal epilepsy. *$p < 0.05$.

Table 2
Adverse events during the course of treatment (N = 149).

AE, n (%)	0–3 months	0–6 months	0–12 months
Dizziness	18 (12.1)	21 (14.1)	23 (15.4)
Irritability	13 (8.7)	19 (12.8)	21 (14.1)
Drowsiness	18 (12.1)	21 (14.1)	21 (14.1)
Anxiety	5 (3.4)	8 (5.4)	10 (6.7)
Fatigue	7 (4.7)	7 (4.7)	9 (6.0)
Memory impairment	4 (2.7)	5 (3.4)	6 (4.0)
Headache	4 (2.7)	4 (2.7)	6 (4.0)
Ataxia	3 (2.0)	4 (2.7)	4 (2.7)
Bodyweight gain	0	1 (0.7)	2 (1.3)
GGT increase	1 (0.7)	1 (0.7)	1 (0.7)
Psychosis	0	1 (0.7)	1 (0.7)
Other	0	3 (2.0)	3 (2.0)

AE, adverse event; GGT, gamma-glutamyl transferase.

Within the first 12 months, 15 patients (10.1 %) discontinued PER due to AEs; irritability was the main AE that led to treatment discontinuation after 3 months of PER treatment (4 %). It was also observed that 26 % of patients with a psychiatric comorbidity discontinued PER treatment versus 5.5 % of patients without a psychiatric comorbidity (p = 0.011).

3.3. Analyses by concomitant anti-seizure drugs

3.3.1. PER with sodium channel blockers (PHT, CBZ, OXC, ESL, LTG and LCM)

After 12 months, a significantly lower proportion of patients treated with sodium channel blockers (SCB) and PER were considered seizure-free (28.8 %, n = 61) compared with patients who received PER plus a concomitant ASD not SCB (57.3 %, n = 88; p = 0.001), or responders (49.4 % PER + SCB vs. 91 % PER + ASD not SCB, p = 0.014; Fig. 3A). The between-group difference in the proportion of seizure-free patients remained significant after performing a logistic regression analysis adjusted for the type, duration and aetiology of epilepsy (OR 0.303, 95 % CI: 0.139–0.660, p = 0.003, baseline characteristics of patients taking SCB are shown in Supplementary Table 2).

There was no statistically significant difference between these groups in the proportion of patients with AEs (p = 0.861) or who discontinued treatment due to an AE (p = 0.063).

3.3.2. PER with synaptic vesicle protein 2A modulators (LEV and BRV)

At the end of 12 months, a similar proportion of patients who received PER in combination with a synaptic vesicle protein 2A modulator (n = 54) were considered seizure free (p = 0.420) or responders (p = 0.529) versus those who received PER in combination with an ASD that did not modulate synaptic vesicle protein 2A (n = 95) (Fig. 3B). Furthermore, there were no statistically significant differences in the proportion of patients with AEs (p = 0.516) or in the proportion of patients that discontinued treatment because of an AE (p = 0.322) between these groups.

3.3.3. PER with gamma-aminobutyric acid analogs (PB and BZD)

Only one patient received PB in combination with PER.

3.3.4. PER with an ASD with other mechanisms of action (GBP, PGB, VPA, TPM, ZNS)

The proportion of patients who received PER plus an ASD with other mechanisms of action (n = 30) and were considered seizure free (p = 0.077) or responders (p = 0.167) was similar to those who received PER in combination with the rest of drugs (n = 119) (Fig. 3C). Furthermore, there were no statistically significant differences in the proportion of patients with AEs (p = 0.307) or in the proportion of patients who discontinued treatment because of an AE (p = 0.529) between these groups.

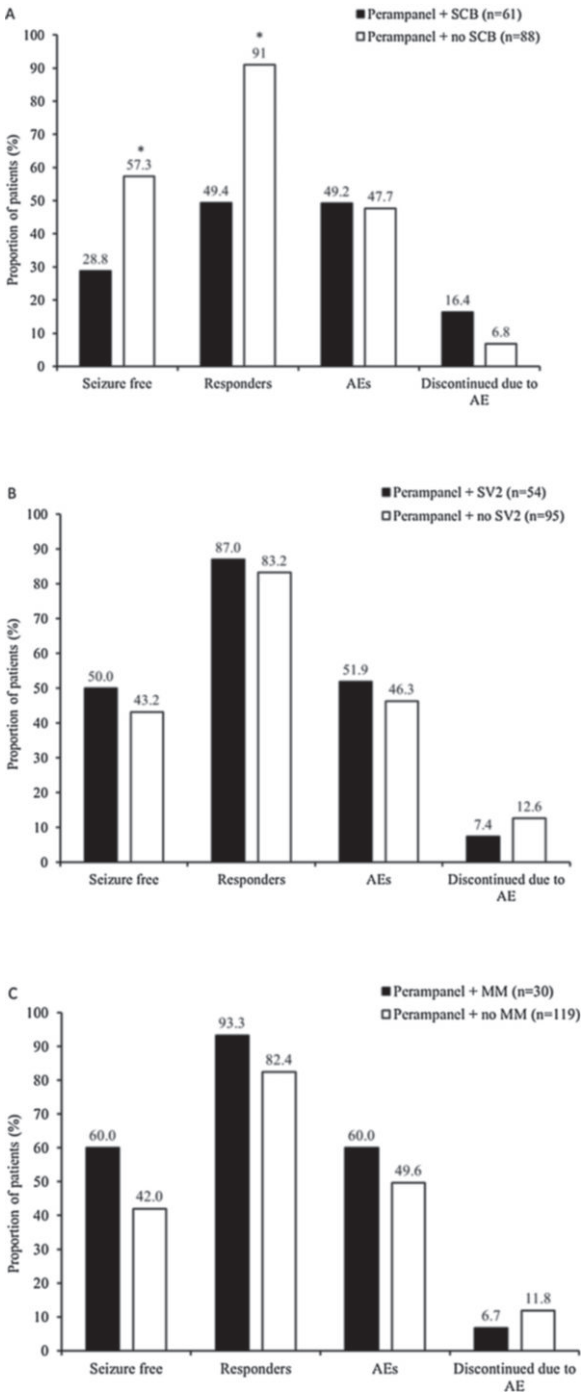

Fig. 3. Efficacy (all seizure types) and tolerability of perampanel as a first add-on therapy at 12 months with or without (A) a sodium channel-blocking anti-seizure drug (eslicarbazepine acetate, lamotrigine, carbamazepine, oxcarbazepine, lacosamide, phenytoin or rufinamide); (B) a synaptic vesicle 2 modulating anti-seizure drug (brivaracetam or levetiracetam); or (C) an anti-seizure drug with other mechanisms of action (miscellaneous mechanisms of action; valproic acid, pregabalin, topiramate or zonisamide). *p < 0.01. AE(s), adverse event(s); MM, miscellaneous mechanisms of action; SCB, sodium channel blocker; SV2, synaptic vesicle 2.

3.3.5. PER with strong enzyme-inducing (CBZ, PB, PHT) or enzyme inhibiting (VPA) ASDs

A lower proportion of patients treated with strong enzyme-inducing ASDs and PER (n = 12) was seizure-free after 12 months compared with patients who received PER plus another concomitant ASD (n = 137) (0

% vs. 49.6 %, p = 0.001; Fig. 4A). No significant differences were found regarding the dose of PER administered in both groups. The worse prognosis of patients treated with strong enzyme-inducing ASDs remained significant after performing a logistic regression analysis adjusted for the type, duration and aetiology of epilepsy (OR 0.079, 95 % CI: 0.009–0.653, p = 0.019); there were no differences in the baseline characteristics of these patients (Supplementary Table 3).

No significant differences in the proportion of patients who were responders, who had AEs or who discontinued treatment due to AEs were found between patients treated with PER in combination with a strong enzyme-inducing ASD and those who received PER in combination with another ASD (Fig. 4A).

The proportion of seizure-free patients was higher in patients treated with the enzyme inhibitor VPA and PER for 12 months (n = 22), compared with patients who received PER plus a different concomitant ASD (n = 127) (68.2 % vs. 42.1 %, p = 0.023; Fig. 4B). There were no differences in the median dose of PER in both groups. This difference was statistically significant, even when adjusted for the type of epilepsy, duration, aetiology and number of previous seizures, which was significantly lower in patients taking the enzyme-inhibiting drug VPA before starting PER treatment (OR 3,549, 95 % CI: 1.033–12.185, p = 0.044). The baseline characteristics of patients taking VPA are shown in Supplementary Table 4.

There was no significant difference in the proportion of patients considered responders in patients treated with PER in combination with the enzyme-inhibiting drug VPA (95.5 %) compared with patients treated with PER in combination with other ASDs (83.3 %, p = 0.199). There were no statistically significant differences in the proportion of patients with AEs (p = 0.824) between these groups and the statistical significance of the difference in the proportion of patients who discontinued treatment because of AEs could not be established.

3.3.6. PER with LEV

After 12 months of treatment, there were no significant differences in the efficacy or tolerability of PER in patients who were receiving concomitant LEV or patients receiving another ASD concomitantly

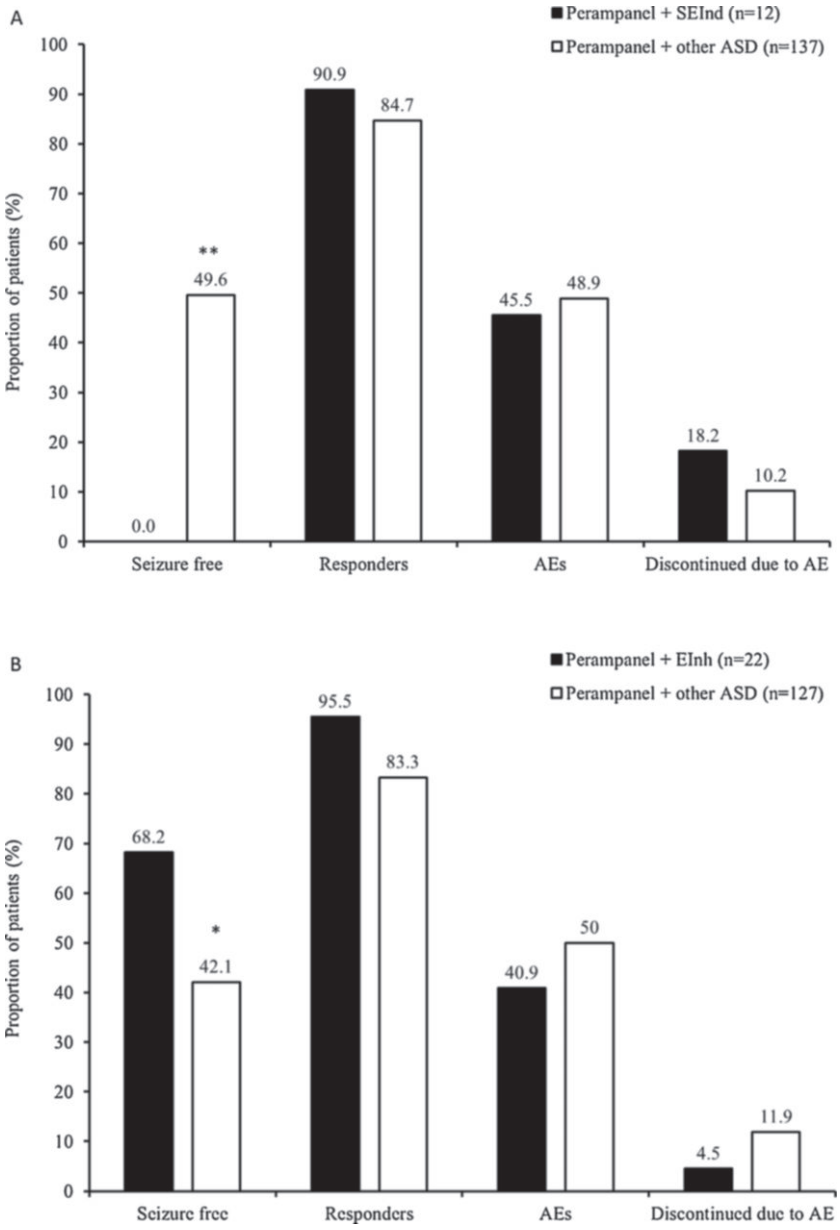

Fig. 4. Efficacy (all seizure types) and tolerability of perampanel as a first add-on therapy with (A) a strong enzyme inducer (SEInd; carbamazepine, phenobarbital or phenytoin) or (B) an enzyme inhibitor (EInh; valproic acid) at 12 months, **p = 0.001; *p < 0.05. AE(s), adverse event(s); ASD, anti-seizure drugs.

(Supplementary Fig. 1).

4. Discussion

This retrospective observational study indicates that, in a real-world clinical practice setting, PER is effective and well tolerated as first add-on therapy in patients with focal epilepsy or IGE who require additional anticonvulsant therapy in combination with their ongoing monotherapy for seizure control. This is also one of the first studies to examine the response of different PER-containing combinations of ASDs. Although the tolerability of PER was consistent regardless of the type of concomitant ASD, worse seizure control was observed when PER was combined with SCB and strong enzyme-inducing ASDs such as CBZ, PB, PHT. In these cases, higher doses of PER may be required to achieve an efficacy that is comparable to PER with other ASDs.

In one large real-world observational study and a pooled analysis of real world data in which PER was not necessarily the first add-on therapy, 35.9 % [38] and 39 % [22] of patients receiving PER had a ≥50 % decrease in seizures at 12 months. In the study by Garamendi-Ruiz et al. [38], in which the majority of patients had focal epilepsy, this response rate increased to 45 % when patients received PER and one other ASD. This is lower than the 12-month response rate seen in our study, and probably reflects differences in patient populations; compared with patients from Garamendi-Ruiz et al., [38] patients in the current study had a shorter duration of epilepsy (mean 9.6 vs 24.6 years) and a higher proportion of patients had primary generalized epilepsy (22.1 % vs 3.9 %).

The response rate in patients with focal epilepsy in our study (82.3 %) was markedly higher than that observed in a real-world study in a large cohort of patients with focal epilepsy (26.8 %). [21] The reasons for this variation are likely due to differences in patient samples; in the FYDATA study, epilepsy was more "pharmacoresistant": patients had received a mean 7.8 previous ASDs [21], compared with a maximum of 3 previous ASDs, as monotherapy, in our study. In addition, the distribution of aetiologies was different (higher proportion of mesial temporal sclerosis or cortical development malformation) and the duration of epilepsy in our study was shorter. Similar reasons may explain the difference with the Rohracher et al. study [22]. As found in a previous real-world study in patients with generalized seizures [39], we found that PER reduced all seizure types in patients with generalized seizures. Our study is consistent with previous studies showing that PER was more effective when used early in the course of treatment [21,38,39], and reduced the number of both generalized and focal seizures [11,21, 38–43].

In our study, the high retention rate observed at 12 months, is consistent with previous real-world observational studies with perampanel, which have generally reported 12-month retention rates of 60.6–85%. [21,23,38,39]

In agreement with previous reports, our study showed a lower response rate when PER was administered with certain ASDs. This likely reflects an effect of these agents on PER pharmacokinetics. PER is rapidly absorbed and peak plasma concentrations occur 0.5–2.5 h after oral ingestion; its bioavailability is ~100 %. [5,6] PER has linear and predictable pharmacokinetics at clinically relevant doses (2–12 mg); it is 95 % protein-bound to albumin and α1-acid glycoprotein [5,6]. Like other ASDs, PER is primarily metabolized in the liver by cytochrome P450 (CYP) 3A4, which could lead to clinically relevant drug interactions. [44]

We observed a reduced rate of seizure control in patients receiving concomitant strong enzyme-inducing ASDs, which could be explained by more rapid hepatic metabolism of PER when administered with these agents. Other real-world observational studies [21,41] have reported reduced response when PER is administered with enzyme-inducing drugs; some have also reported a need for higher PER dosages and a reduced incidence of AEs with such combinations [21,38,45,46], consistent with a pharmacokinetic interaction. In our study, greater seizure control was also observed when PER was administered with ASDs that do not block sodium channels, probably because some SCB are also strong or moderate enzyme-inducers [27] and could lead to a reduction of PER levels. Thus, our findings support further exploring the use of higher PER doses with strong enzyme-inducing ASDs.

A pharmacokinetic simulation study, which used data from clinical trials, confirmed that, in the presence of an enzyme-inducing ASD, PER had a lower plasma concentration and a higher fluctuation index. [47] Furthermore, the effect of a missed PER dose on plasma exposure is exacerbated by a concomitant enzyme-inducing ASD, meaning PER dose replacement is recommended in patients taking these drugs together. [47].

Another interesting finding is the greater response observed in patients receiving PER and VPA. Although the numbers are small, the effect seems to be unrelated to the type of epilepsy or to PER dose. This could be due to a possible pharmacokinetic interaction between both drugs leading to an increase in the plasma concentration of PER in the presence of VPA, as reported previously [48]. PER undergoes metabolism primarily by CYP3A4/A5 isoforms, and VPA has a mild inhibitory effect on these isoforms. However, the contribution of isoforms other than CYP3A4/A5 cannot be excluded.

Perampanel showed good efficacy and tolerability when administered as a first add-on to patients taking LEV (one of the most commonly used ASDs), suggesting that PER is a good add-on option in this setting.

Approximately 50 % of patients in our study reported an AE with PER, similar to rates of 35.5–68 % reported in other real-world studies. [21,22,38,39,41,43,49] The common AEs reported in our study are consistent with those reported elsewhere with PER [5,6,9], and no new safety signals were identified. The transient nature of certain AEs with PER observed in our sample has also been reported previously [50]. In our study, irritability was the most common AE leading to discontinuation; this contrasts with data from phase III studies showing that the most frequent AEs with PER were dizziness, somnolence, and headache [51].

Although previous psychiatric comorbidities seem to be a risk factor for increased incidence of AEs with PER treatment, concomitant ASDs did not affect the tolerability of PER in the current study and adding PER did not seem to have significant effects on psychiatric comorbidities. These results support previous real-world findings where PER as a first add-on therapy did not affect AEs related to hostility [21,23,39,41] and had no [23] or minimal effect on AEs related to aggression [21,39,41]. In our study, however, the assessment of psychiatric AEs was limited as no Hospital Anxiety and Depression Scale scores were collected.

Strengths of this study include the large number of participating centres (n = 22) and patients (n = 149) and the real-world clinical setting. However, there are limitations inherent in the retrospective, observational study design, including the lack of a control group and the potential for selection bias. Some of our subgroup analyses used small patient numbers, so between-group results should be interpreted with caution. In addition, because we relied on clinical records for data, there was no information of plasma PER levels to establish whether they were affected by concomitant ASDs.

5. Conclusion

This is the first study in a real-world setting to examine the effects of PER with other ASDs to determine the most effective combination. In clinical practice in Spain, PER was effective and safe as a first add-on therapy in patients with non-refractory focal epilepsy or IGE. Perampanel was well tolerated regardless of the concomitant ASDs administered. A higher efficacy was found when PER was given in combination with VPA; conversely, a lower efficacy was observed when PER was combined with a strong enzyme-inducing or sodium channel-blocking ASD. These findings support further research into PER dose adjustment according to the mechanism of action of concomitant ASDs to optimize seizure control.

Author contributions

Estevo Santamarina Pérez was involved in the collection and analysis of data in this study as well as reading and approving the drafts of the manuscript.

Vicente Bertol Alegre was involved in the collection and analysis of data in this study as well as reading and approving the drafts of the manuscript.

Vanesa Garayoa Irigoyen was involved in the collection and analysis of data in this study as well as reading and approving the drafts of the manuscript.

María José García Gomara was involved in the collection and analysis of data in this study as well as reading and approving the drafts of the manuscript.

Iñigo Garamendi-Ruiz was involved in the collection of data in this study as well as reading and approving the drafts of the manuscript.

Pau Giner Bayarri was involved in the collection and analysis of data in this study as well as reading and approving the drafts of the manuscript.

Inés Aranzábal Alustiza was involved in the collection and analysis of data in this study as well as reading and approving the drafts of the manuscript.

Anna Piera Balbastre was involved in the collection and analysis of data in this study as well as reading and approving the drafts of the manuscript.

Carolina Arcos Sanchez was involved in the collection and analysis of data in this study as well as reading and approving the drafts of the manuscript.

Patricia Esteve Belloch was involved in the collection and analysis of data in this study as well as reading and approving the drafts of the manuscript.

Ainhoa Marinas Alejo was involved in the collection and analysis of data in this study as well as reading and approving the drafts of the manuscript.

Alejandro García Escrivá was involved in the collection and analysis of data in this study as well as reading and approving the drafts of the manuscript.

Alejandro Viloria-Alebesque was involved in the collection of data as well as reading and aproving the final draft of the manuscript.

Fernando Ayuga Loro was involved in the collection and analysis of data in this study as well as reading and approving the drafts of the manuscript.

Alejandro Ponz de Tienda was involved in the collection and analysis of data in this study as well as reading and approving the drafts of the manuscript.

José Antonio Olivan Usieto was involved in the collection and analysis of data in this study as well as reading and approving the drafts of the manuscript.

Macarena Bonet Valls was involved in the collection and analysis of data in this study as well as reading and approving the drafts of the manuscript.

Pablo Dávila-González was involved in the collection and analysis of data in this study as well as reading and approving the drafts of the manuscript.

Rafael Sivera Mascaró was involved in the collection and analysis of data in this study as well as reading and approving the drafts of the manuscript

Albert Molins Albanell was involved in the collection and analysis of data in this study as well as reading and approving the drafts of the manuscript.

Gemma Sansa Fayos was involved in the collection and analysis of data in this study as well as reading and approving the drafts of the manuscript.

José Carlos Roche Bueno was involved in the collection and analysis of data in this study as well as reading and approving the drafts of the manuscript.

Ana Belén Martínez was involved in the collection and analysis of data in this study as well as reading and approving the drafts of the manuscript.

Sandra Monteagudo was involved in the collection and analysis of data in this study as well as reading and approving the drafts of the manuscript.

Teresa Casadevall was involved in the collection and analysis of data in this study as well as reading and approving the drafts of the manuscript.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Declaration of Competing Interest

None.

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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.seizure.2020.09.026.

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