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Perampanel as add-on therapy in epilepsies with known etiology: A single center experience with long-term follow-up

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ABSTRACT

We report a retrospective monocentric study performed on 63 patients affected by epilepsy with known etiology, receiving perampanel as add-on therapy with at least 12-month follow-up. The purpose of our study was to evaluate efficacy and tolerability of perampanel in this group of epilepsies. Patients were classified into 2 groups based on the presence/absence of a single focal brain lesion on MRI, as epilepsy etiology: 48 subjects were affected by focal lesional epilepsy and 15 by non-focal lesional epilepsy. The retention rate was 76.2% and 53.9% at 12 and 24 months respectively. At 12 months, at least 40% of patients resulted responders, with a significant reduction in seizure frequency ($p = 0.01$), confirmed at 24 months. Considering epilepsy etiology, we found a better PER response in patients with focal lesional epilepsy. A significant correlation was observed between responder rates and EEG pattern. Only 30% of patients reported mild-moderate adverse events. Efficacy and tolerability of PER, in our study, are in line with the results reported in other real-world studies. Our data suggest the possibility of better PER response in patients with focal brain lesions, which indicates that this drug could be a therapeutic option in this population.

Introduction

Epilepsy is one of the most common chronic neurological disorders, affecting 1–2% of the general population worldwide [1]. Despite the availability of as many as 28 different anti-seizure medications (ASMs) [2], up to 30% of epileptic patients remains resistant to medical treatment [3].

The etiology of epilepsy is a strong prognostic predictor for seizure recurrence and for subsequent drug-resistance. In particular, people with epilepsies due to known etiology show a lower chance of remission [4] and need long-term pharmacological treatment. Thus, it is important to identify safe, well-tolerated and effective drugs, particularly in the setting of add-on therapy [4].

Perampanel (PER) is a non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazole-proprionic acid (AMPA) receptor antagonist. Therapeutic efficacy and safety of PER had been demonstrated in four phase III trials [5–8] and confirmed by several post-marketing studies [9–11].

Our purpose was to evaluate both perampanel efficacy and tolerability, in a population with epilepsy due to known etiology, and which type of seizure or epilepsy better responds to PER.

Material and methods

Study design

This is a retrospective monocentric long-term observational study, conducted in a real-world setting. Patients were enrolled among those attending the outpatient service of the Neurological Unit of "Santa Maria della Misericordia" University Hospital in Udine (Italy), between January 1st, 2015 and December 31st, 2018.

Abbreviations: AE, adverse event; ASM, anti-seizure medication; CTCAE, Common Terminology Criteria for Adverse Events; EEG, electroencephalogram; EiASM, enzyme-inducing anti-seizure medication; ILAE, International League Against Epilepsy; MRI, Magnetic Resonance Imaging; PER, perampanel; TLE, temporal lobe epilepsy.

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Inclusion criteria were: age ≥ 18 years old; diagnosis of epilepsy with a known etiology; treatment with PER according to approved indications; a clinical follow-up of at least 1 year. According to the International League Against Epilepsy (ILAE) classification [12], we considered epilepsies with known etiology including structural, genetic, infectious, immune-mediated and metabolic causes. Diagnosis was made on clinical, electroencephalographic (EEG) and neuroradiological features. For the analysis purpose, patients were classified into two groups based on the presence or absence of a single focal brain lesion on MRI, recognized as associated to epilepsy. In particular, patients with a structural brain lesion were included in the first group (defined as "focal lesional epilepsy"). The second group (defined as "non-focal lesional epilepsy") comprised patients with known etiology and negative MRI, and/or subjects with known etiology and evidence of diffuse cerebral damage at MRI.

Patients who did not attend regularly our outpatient service or with unreliable clinical records were excluded.

Data collection

Data were collected from patients' medical records and seizure diaries.

The following data were collected at baseline: demographics, age at epilepsy onset, epilepsy duration, seizure type, etiology, number of concomitant and previous ASMs.

Seizure frequency was calculated at baseline, at visit (V) 6, V12 and, when possible, at V24, as mean seizures per month.

For the analysis, we considered beneficial effects lasting six months or longer, to avoid regression to the mean [13].

During each visit, blood test (complete blood count and biochemistry) was performed and data were extracted.

EEG recordings, performed in the 6 months before PER starting, were collected.

Each EEG was performed during full wakefulness, with a 32-channel machine (*EB Neuro Mizar Sirius system with Galileo NT software, EB Neuro*), with electrodes placed according to the 10–20 International System. Recordings were routinely carried out for 20 minutes, with hyperventilation and photic stimulation. Low frequency filter was set at 0.3 Hz, high frequency filter at 70 Hz; and sensitivity was 70 microV/mm.

EEGs were separately analyzed off-line by two neurophysiologists (G. P. and A. N.). In case of discordance, a final review of EEG traces was performed by the two neurophysiologists together, until a common decision was obtained.

EEG recordings were scored according to the presence of slow and/or epileptiform activity.

We identified 6 patterns:

1) unilateral focal slow theta activity;
2) unilateral focal slow theta activity with superimposed sharp waves;
3) unilateral focal epileptiform activity;
4) bilateral focal epileptiform activity;
5) diffuse epileptiform activity;
6) normal (alpha rhythm as background without slow or epileptic activity).

Study variables

The primary efficacy endpoints were: 1. the retention rate at 12 months and at 24 or more when applicable; 2. the proportion of patients with ≥50% reduction in seizure frequency compared to baseline (50% responder rate), observed at 12 and 24 months; 3. the proportion of patients free of all seizure types at 12 and 24 months. Secondarily, we considered the proportion of patients free of focal seizures and the proportion of subjects free from focal to bilateral tonic-clonic seizures. Seizure freedom was defined as the absence of seizures since the baseline visit, when PER was started. Changes in seizure frequency at 12 and 24 months were considered for the analysis.

Safety end points included: 1. the proportion of patients with AEs at 6 and 12 months, and 24 months if available; 2. adverse event (AE) severity, graded according to Common Terminology Criteria for Adverse Events (CTCAE); 3. the proportion of patients with AEs that lead to discontinuation at each visit.

Several clinical characteristics were compared: focal lesional epilepsy vs. non-focal lesional epilepsy; focal seizures vs. focal to bilateral tonic-clonic seizures; EEG patterns; early PER add-on (0–2 previous ASMs, including current ASMs) vs. late PER add-on (≥3 previous ASMs); patients receiving vs. not-receiving concomitant enzyme-inducing ASMs (EiASMs).

Statistical analysis

All data were collected in an ad hoc created database (Excel 2013, Microsoft Corp., Redmond, WA, USA). Data cleaning was performed before the data analysis. The average imputation method and the last observation carried forward method were used to handle missing values (<5% of missing data).

Continuous variables were summarized by descriptive statistics, expressed as median, arithmetic mean, standard deviation and range, and categorical variables by absolute frequencies and percentages.

In the efficacy analyses, variations in the frequency of seizures were analyzed using Wilcoxon test for not normally distributed data. For all subgroups analyses we used Chi-Square test (or Fisher's exact test) to compare categorical variables, and McNemar test for continuous variables.

Statistical analyses were performed using SPSS version 25 (IBM Corporation, Chicago IL, USA).

Results

Patients' characteristics, disposition and retention rate

Sixty-four (72.7%) out of 88 patients receiving a prescription for PER fulfilled the inclusion criteria. One patient was excluded because of death due to disease progression (primary brain tumor), 3 months after starting PER therapy.

Among the 63 enrolled patients (32 females and 31 males, mean age at PER onset: 45.8 ± 12.8 years, age range: 21–76 years), 48 (76.2%) were affected by epilepsy due to focal lesion, while 15 (23.8%) by non-focal lesional epilepsy.

Main demographic variables and etiology are reported in the Table 1.

All patients had a 12 months clinical follow-up; for 39 of them (61.9%) a follow-up of 2 years was also available.

The retention rate was 76.2% and 53.9% at 12 and 24 months respectively.

The mean (±SD) perampanel dose was 5.9 ± 1.93 mg at 6 months, 6.9 ± 1.85 mg at 12 months and 7.8 ± 1.98 mg at 24 months. Subjects taking at least one EiASMs at the time of PER initiation attained a higher maximum perampanel dose compared to those with a non-EiASMs (7 mg vs. 5.9 mg, respectively, $p = 0.04$).

The mean duration of perampanel exposure was 23.7 ± 14.06 months (range: 6–48 months).

At 12-months follow-up, 15 patients discontinued PER, while at 24-months 5 more patients withdrew the drug.

Table 1
Demographics and clinical characteristics of the patients.

Variables	Perampanel n = 63
Gender, n (%)	
Male	31 (49.2)
Female	32 (50.8)
Median age at epilepsy onset, years (IQR)	18 (0–72)
Median duration of epilepsy, years (IQR)	26 (1–60)
Mean age at perampanel onset, years (range)	45.8 (21–76)
Median number of previous (excluding current) ASMs (IQR)	3 (0–9)
Median number of concomitant ASMs (IQR)	2 (1–5)
Early add-on, n (%)	14 (22.2)
Late add-on, n (%)	49 (77.8)
Concomitant EiASMs, n (%)	34 (54)
1 EiASMs	26 (41.3)
>1 EiASMs	8 (12.7)
Concomitant non-EiASMs, n (%)	29 (46)
Epilepsy with known etiology, classification	
Focal lesional epilepsy, n (%)	48 (76.2)
Cortical malformations	23 (36.5)
Arteriovenous malformations	3 (4.8)
Tumor-related	13 (20.6)
Post-traumatic	9 (14.3)
Non-focal lesional epilepsy, n (%)	15 (23.8)
Diffuse cerebral microangiopathy	8 (12.7)
Genetic (channelopathies)	3 (4.7)
Infective	2 (3.2)
Immune (Ab anti-CASPR2 and anti-LGI1)	2 (3.2)
Temporal lobe epilepsy, n (%)	28 (44.4)
Non-temporal lobe epilepsy, n (%)	35 (55.6)
Seizure type at PER onset, n (%)	
Focal seizures	32 (50.8)
Focal to bilateral tonic-clonic seizures	6 (9.5)
Focal seizures + focal to bilateral tonic-clonic seizures	25 (39.7)

Legend: IQR = interquartile range; ASMs = antiseizure medications; EiASMs = enzyme-inducing antiseizure medications.

Discontinuation of PER was due to lack of efficacy (10 patients), occurrence of AEs (5 patients) and both conditions (5 subjects).

Treatment response

Seizure frequency change and response

At 12 months, 39.7% (25/63) of subjects showed a significant reduction in all seizure frequency (p = 0.01, Wilcoxon test) with an average relative reduction in seizure frequency of 35.7%. Ten patients (15.7%) were seizure-free. This statistically significant reduction of seizure frequency was confirmed at 24 months (p = 0.001, Wilcoxon test). After 24 months of treatment, 9 patients were seizure-free and 13 subjects (33.4%) showed a reduction of seizure frequency $\geq$ 50%.

A sub-analysis of seizure types showed a significant reduction of both focal seizures and focal to bilateral tonic-clonic seizures frequency from baseline to 12 months (p = 0.002 and p = 0.005, respectively, Wilcoxon test). At 24 months, only focal to bilateral tonic-clonic seizures retained a significant reduction in frequency (p = 0.01) (Fig. 1). Focal to bilateral tonic-clonic seizures displayed a better trend to improve then focal seizures, both at 12 and 24 months (p = 0.06, McNemar test).

Considering the etiology of epilepsies, patients with a brain focal lesion showed a better PER response at 12 and 24 months (p = 0.03 and p = 0.02 respectively, Chi-square test) as showed in Table 2.

Focusing on specific clinical variables, we observed better seizure outcomes in patients with epilepsy duration < 20 years (p = 0.02, Chi-square test), and in patients who took PER as early add-on (p = 0.02, Chi-square test).

At 12 months, the efficacy of PER was greater in association with the use of concomitant non-EiASMs (p = 0.05, Fisher's test).

EEG patterns

Unilateral focal epileptiform activity (pattern 3) was the most frequently observed in our sample (36.5%, 23/63). Several patients presented a combination of 2 different EEG patterns. Pattern 2 (unilateral focal slow theta activity with superimposed sharp waves) was significantly associated to a better responder rate, both at 12 and 24 months of follow-up (p = 0.005 and p = 0.01 respectively, Fisher's exact test).

Stratifying patients on the basis of etiology and comparing the etiology to EEG patterns, we found that pattern 2 was present only in patients with focal lesional epilepsy: 7 patients with tumor-related epilepsy, 6 with epilepsy associated to cerebral malformations and 3 with post-traumatic epilepsy. An additional sub-analysis was performed and it showed a better, even if not statistically significant, seizures outcome in patients with tumor-related epilepsy (p = 0.09, Fisher's exact test). The distribution of EEG patterns and seizures outcome are summarized in Table 3.

Safety and tolerability

By 12 months, 30.2% (19/63) of patients had reported at least one AE, and seven of them (11.1%) at least 2 different AEs. Most AEs occurred within the first 3–6 months of therapy (16/63, 25.4%). In fact, at 24 months, only three additional patients experienced a late AE.

All reported AEs were mild (grade 1) or moderate (grade 2), like irritability (17.2%), psychomotor delay (25.8%) and dizziness (17.2%). Only one patient experienced a grade 3 AE, consisting in a cutaneous rash that remitted after PER discontinuation. Severe psychiatric symptoms were not reported. The rate of psychiatric AEs was not statistically increased in patients taking topiramate or levetiracetam or both, compared to other drug combinations. No alterations of laboratory parameters have been observed.

The incidence of AEs was significantly influenced only by the use or not of concomitant EiASMs (p = 0.04, Chi-square test).

Discussion

We investigated the efficacy and safety of PER in a retrospective real-life study, finding that patients with focal lesional epilepsy and those with a specific EEG pattern (unilateral focal slow theta activity with superimposed sharp waves) represent the group more likely to benefit from this ASM. These findings are relevant as they address a common clinical problem, namely the management of lesional epilepsy, which is complicated by polytherapy, drug-to-drug interactions, limitations in ASMs use and comorbidities. The direct consequence of these issues is a greater intrinsic risk of drug-resistance and AEs development, which strongly affects the therapeutic choice, thus calling attention on a more "targeted" approach. In addition, our study shows the overall efficacy and safety of PER, providing also a higher retention rate (76.2% and 53.9% at 12 and 24 months, respectively) as compared to previous real-world studies (50.5% to 60.6%) [11,14,15], despite a lower mean dose of the drug [11,14,15]. A statistically significant reduction of seizure frequency both at 12 and 24 months was observed. Seizure freedom was achieved in 15.7% patients at 12 months and in 14.3% patients at 2 years. As reported in the randomized controlled trials (RCTs) [5–8] and in two real-world studies [11,16], focal to bilateral tonic-clonic seizures showed a better clinical response maintaining a statistically significant improvement at 12 and 24 months. This could be explained by the reduction of seizure propagation due to the antagonism of AMPA receptor exerted by PER [17] and it may suggest the use of perampanel in patients with focal to bilateral tonic-clonic seizures. Greater efficacy of PER in focal lesional epilepsy may depend on

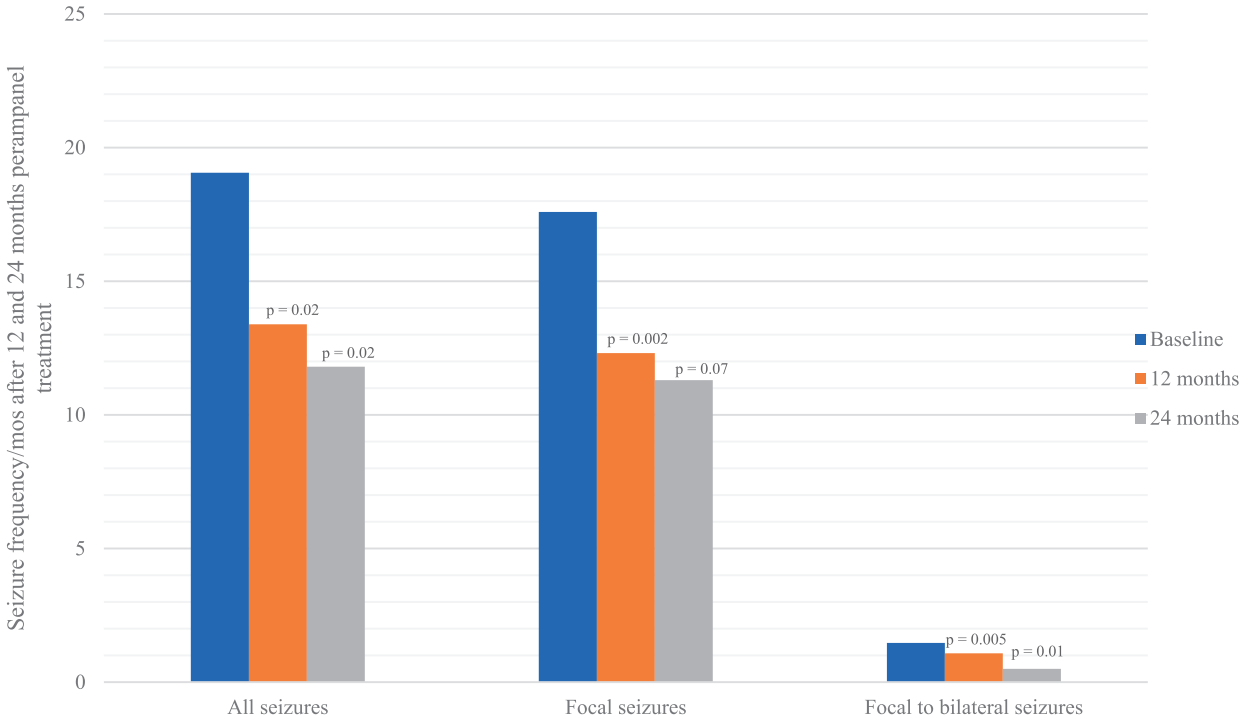

Fig. 1. Changes in seizure frequency/mos with perampanel at 12 and 24 months relative to baseline by seizure type.

Table 2
Responder rate in focal lesional vs. non-focal lesional groups.

	12 months (*n* = 63)		24 months (*n* = 39)	
	Focal lesional epilepsy *n* (%)	Non-focal lesional epilepsy *n* (%)	Focal lesional epilepsy *n* (%)	Non-focal lesional epilepsy *n* (%)
Responder rate	17 (26.9%)	8 (12.7%)	13 (33.4%)	9 (23.0%)
Responder 50–99%	8 (12.7%)	7 (11.2%)	5 (12.8%)	8 (20.5%)
Seizure-free	9 (14.2%)	1 (1.5%)	8 (20.5%)	1 (2.5%)
Non Responder	31 (49.1%)	7 (11.2%)	12 (30.8%)	5 (12.8%)
Total	48	15	25	14

Table 3
EEG patterns and responders' correlations.

Pattern EEG	*n* (%)	Responders (total *n* = 25) 12 months		Responders (total *n* = 22) 24 months	
		n (%)	*p-value*	*n* (%)	*p-value*
Type 1	17 (26.9)	6 (24)	0.76	5 (22.7)	0.55
Type 2	16 (25.4)	10 (40)	0.005[a]	9 (40.9)	0.01[a]
Type 3	23 (36.5)	5 (20)	0.17	4 (18.3)	0.21
Type 4	6 (9.5)	3 (12)	0.23	2 (9.1)	0.29
Type 5	6 (9.5)	1 (4)	0.38	1 (4.5)	0.23
Type 6	7 (11.2)	0 (0)	0.72	1 (4.5)	0.42

[a] Fisher's exact test: statistically significant.

the role of glutamatergic transmission in the pathological mechanisms of tumor-related epilepsy, post-traumatic epilepsy and structural temporal lobe epilepsy, as demonstrated by preclinical and clinical evidences [18–20]. In fact, in brain tumor-related epilepsy, alteration of glutamate homeostasis induces an increased excitotoxicity which promotes migration and expression of tumor cells. Moreover, increased glutamate production leads to neuronal hyperexcitability in the neural tissue surrounding the tumor; all these processes contribute to maintain and propagate epileptic activity [18–19]. Glutamate plays a central role also in the pathophysiology of traumatic brain injury and subsequent process of epileptogenesis [21].

Finally, our data indicate that PER was globally well tolerated, with side effects which tend to subside over time. Concomitant use of non-EiASMs emerged as the only risk factor for increased AEs rate.

Limitations

This is a retrospective study, thus it presents all limitations intrinsic to this kind of observations (lack of randomization and control group, risk of missing relevant information). We acknowledge that the sample is limited, since we focused on epilepsy due to known etiology.

Moreover, we considered a different and heterogeneous type of etiology that limits the generalization of our results.

Finally, it comes from a single center, a guarantee of homogeneity, but also a risk of unintended biases.

Conclusions

Our study suggests that patients with focal lesional epilepsy and those with a distinct EEG pattern (unilateral focal theta activity with superimposed sharp waves) may represent the group most likely to favorably respond to PER. These results need future validation in multicenter trials adopting a clinical stratification based on neuroimaging and EEG data.

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All co-authors have been substantially involved in the study and preparation of the manuscript. All co-authors have approved the submitted version of the paper and accept responsibility for its content.

Data access, responsibility, and analysis

The Corresponding Author had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Declarations of interest

None.

Compliance with ethical standards

All procedures were performed in accordance with the institutional ethics committee and the Declaration of Helsinki.

Conflict of interest

All authors report no conflicts of interest.

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