Epilepsy & Behavior 98 (2019) 139–144

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Efficacy and impact on cognitive functions and quality of life of perampanel as first add-on therapy in patients with epilepsy: A retrospective study

Raffaele Rea [a], Enea Traini [b], Rosaria Renna [a,*], Francesco Pagliuca [c], Marianna Pezzella [a], Mauro Pagliuca [a]

[a] U.O.C. di Neurologia, A.O.R.N. "A. Cardarelli", Napoli, Italy
[b] Centro di Ricerche cliniche, Telemedicina e Telefarmacia, Università degli Studi di Camerino, Macerata, Italy
[c] Clinica Neurologica, Università "L. Vanvitelli", Napoli, Italy

ARTICLE INFO

Article history:
Received 3 April 2019
Revised 30 June 2019
Accepted 3 July 2019
Available online 30 July 2019

Keywords:
Perampanel
Cognitive dysfunction
Quality of life
Seizure

ABSTRACT

Cognitive dysfunctions are frequent in patients with epilepsy. This comorbidity significantly alters their quality of life and plays an important role in their therapeutic management. Perampanel is a noncompetitive antagonist of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors and is considered a new generation AED (antiepileptic drug) with limited impact on cognitive functions.The aims of this study were to evaluate the efficacy of perampanel as first add-on therapy and its impact on cognitive functions and quality of life in patients with epilepsy followed for 6 months at the Neurology Division of "A. Cardarelli" Hospital in Naples (Italy).

1. Introduction

Cognitive dysfunction is frequent in patients with epilepsy. This comorbidity significantly alters their quality of life (QOL) and plays an important role in their therapeutic management [1]. Several factors contribute to the development of cognitive dysfunctions, among them are the following: age of onset, type of syndrome, etiology, frequency, seizure duration and seriousness, and antiepileptic drugs' (AEDs) side effects [2]. Sedation, memory disorders, and attentional deficits have frequently been observed during antiepileptic therapies [3]. In this regard, several meta-analyses show that new generation drugs may have a better cognitive profile as compared to older drugs [4,5]; however, it is still difficult to definitely identify the causal relationship between the pharmacological treatment and the genesis of cognitive dysfunctions [5–7]. Perampanel (PER, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA]) is a noncompetitive antagonist of AMPA receptors and has been approved as adjunctive therapy for partial-onset seizures with or without secondary generalization, and for generalized-onset seizures in adult with epilepsy and adolescent patients from 12 years of age [8–10]. Perampanel is considered a new generation AED with limited impact on cognitive functions [4]. Its medium and long-term cognitive effects were analyzed in a 19-week randomized, controlled, double-blind trial that enrolled children and teenagers (12–18 years of age) [11], followed by a 52-week open-label extension phase [12]. In both double-blind and open-label phases, PER had limited impact on cognitive functions, with statistically significant values only in attention deficit [11,12]. A more recent retrospective naturalistic study compared cognitive side effects of PER and lacosamide (LCS) in 94 adult patients for 36 weeks, and showed no negative effects on cognitive functions [13]. There are no studies in literature on the cognitive effects of PER as first add-on therapy in adults with epilepsy. The aims of this study were to evaluate the efficacy of PER as first add-on therapy and its impact on cognitive functions and QOL in patients with epilepsy followed for 6 months at the Neurology Division of "A. Cardarelli" Hospital in Naples (Italy). The study was approved by the local Ethics Committee.

2. Methods

2.1. Study design and data collection

The study included patients treated with PER as first add-on therapy for the control of epileptic seizures from July 2015 to December 2016. Patients' clinical data (age, gender, disease duration, type of epileptic syndrome, type of seizures, concomitant pathologies, previous pharmacological treatment, daily record of seizures, neurological and neuropsychological evaluations, and instrumental data) were retrieved from patients' medical records of the epilepsy outpatient clinic and recorded into an electronic form for statistical analysis. Patients on epileptic polytherapy at the time of PER addition

* Corresponding author.
E-mail addresses: rosrenna@yahoo.it, rosaria.renna@aocardarelli.it (R. Renna).

https://doi.org/10.1016/j.yebeh.2019.07.005
1525-5050/

Table 1
Patients' clinical and demographic characteristics.

Mean age		37.5 years (range: 20–56)
Educational level		10.59 years (range: 5–15)
Epilepsy diagnosis		
Idiopathic		7 (25.9%)
Lesional		8 (29.6%)
Cryptogenic		12 (44.4%)
Mean length of illness		13.7 years (range: 2–50)
Idiopathic		9.7 years (range: 5–15)
Lesional		14.4 years (range: 2–50)
Cryptogenic		15.2 years (range: 2–40)
Type of seizure		Mean at baseline
PCS (40.74%)	11 pts	54.9 ± 33.8
SGS (44.44%)	12 pts	14.3 ± 23.1
PGS (11.11%)	3 pts	13.6 ± 7.5
Absence (3.74%)	1 pt	120 ± 120
Total median seizure frequency at baseline		12
AEDs at baseline		Mean dose (range) in mg/day
ZNS (2 pts)		400 (300–500)
LEV (9 pts)		1861 (1000–3000)
CBZ (2 pts)		1000 (800–1200)
OXA (5 pts)		1340 (1200–1600)
VPA (4 pts)		1450 (1300–1500)
LCS (3 pts)		350 (300–400)
TPM (2 pts)		100 (100)
PER titration		
17 pts		2 mg/2 weeks
8 pts		2 mg/1 week
2 pts		2 mg/4 weeks
PER dose at 3 months		
2 mg		3 pts
4 mg		17 pts
6 mg		6 pts
8 mg		1 pt
PER dose at 6 months		
2 mg		1 pt
4 mg		9 pts
6 mg		4 pts
8 mg		3 pts
10 mg		1 pt

PCS: partial complex seizures; SGS: secondarily generalized seizures; PGS: primarily generalized seizures; ZNS: zonisamide; LEV: levetiracetam; CBZ: carbamazepine; OXA: oxcarbazepine; VPA: valproic acid; LCS: lacosamide; TPM: topiramate.

and patients without a complete neuropsychological assessment before and at least 3 months after PER administration were excluded from the study. Patients with a systemic or progressive neurological condition that could significantly interfere with QOL or with the results of the neuropsychological testing were not included in the study either. Data collection was performed 3 months before PER administration and at 3 and 6 months during the follow-up. Diagnosis and classification of epilepsies followed the principles of the 1989 International League Against Epilepsy (ILAE) classification of epilepsy [14].

Table 2
Efficacy characteristics and mean frequency of seizures with statistical significance.

Evaluation	3 months	6 months
Retention rate	23 (85%)	18 (67%)
Nonresponders	6 (22.2%)	2 (7.4%)
Responders	17 (62.9%)	16 (59.2)
Seizure-free	9 (33.3%)	6 (22.2%)
Median frequency of seizures per month	0*	2.5*

Responder: patient with a reduction of seizures of ≥50% in the previous 3 months.
The table shows the total number of seizures compared to the mean values of seizures at baseline.
* Reduction in the number of seizures is significant with a $p < 0.05$ according to Friedman's nonparametric test.

2.2. Objectives

The primary objective was to evaluate PER efficacy as first add-on therapy and its impact on cognitive functions and QOL after 6 months. Secondary objective was to assess tolerability.

For the evaluation of therapeutic efficacy, patients having seizure reductions of ≥50% were considered responders; those having no seizures were considered seizure-free. The impact on cognitive functions was evaluated by neuropsychological assessments repeated every 3 months from the start of PER therapy. Information on tolerability was collected from clinical records and coded according to the Liverpool Adverse Event Profile (LAEP) [15].

2.3. Neuropsychological evaluation

All patients underwent an extensive neuropsychological testing including tests for memory and attention, frontal functions, praxia, and intelligence or logical-abstractive reasoning testing. The Italian version of Rey Auditory Verbal Learning Test [16] was used to test verbal memory, the Tapping Test of Corsi [17] for visual spatial memory, the short version of the Stroop Test [18] for selective attention, and the Trail Making Test [19] for divided attention and motor speed. The Frontal Assessment Battery [20] was administered to test frontal functions, the Word Fluency tests [21] to evaluate the ability to access the lexicon, and the Rey Complex Figure [22] to evaluate praxic-constructional abilities. Furthermore, the logical reasoning abilities and intelligence were examined with the Colored Progressive Matrices [23]. Finally, the QOLie 31 (QOL in Epilepsy Inventory) [24], a health-related QOL survey for adults (18 years or older) with epilepsy, was administered to all patients. It includes 31 items divided into 7 subscales evaluating emotional well-being, social functioning, energy/fatigue, cognitive functioning, worries about seizures, medication effects, and general QOL. The total score is obtained from a weighted average of the different subscale scores. The tests used in the present study have been found suitable in previous studies to report cognitive changes during antiepileptic therapy in patients with similar characteristics [25].

2.4. Statistical analysis

Results were analyzed by "per protocol" approach with the Statistical Package for Social Science (SPSS14.0). Friedman's nonparametric test was used to compare the variations in the number of seizures during the treatment period. Additionally, Student's *t* analysis for repeated measurement was used to determine possible significant changes in the neuropsychological evaluation and QOL over time. Moreover, a one-way analysis of variance (ANOVA) was performed to find out whether the cognitive variables and the QOL are influenced by the response to treatment (responders vs nonresponders) and by the different types of baseline treatment.

3. Results

Of the 44 patients with epilepsy that received adjunctive treatment with PER in our center from July 2015 to December 2016, 27 met the inclusion criteria, while 17 patients were excluded: 12 because of antiepileptic polytherapy, 3 because of a follow-up period shorter than 3 months, and 2 because of lack of neuropsychological evaluations. Perampanel was prescribed to 27 patients (17 females, 10 males) as first add-on therapy. Two patients out 27 were previously treated with other AEDs: one patient was treated with valproic acid (VPA) + metinal-Idantoin L and one patient with levetiracetam (LEV) + VPA. Perampanel was added after a 3-week washout of metinal-Idantoin L and VPA. The mean age was 37.5 years (range: 20–56), and the mean disease duration was 13.7 years: 9.7 years for patients with idiopathic epilepsy, 14.4 years for patients with lesional epilepsy, and 15.2 years for patients with cryptogenic epilepsy. Patients were treated with once daily PER ranging from 2 to 10 mg. The initial dosage was

2 mg/day and titrated as follows: 2 mg/2 weeks in 17 patients, 2 mg/1 week in 8 patients, and 2 mg/4 weeks in 2 patients. Out of all patients, 8 (29.6%) had symptomatic epilepsy; 7 (25.9%) had idiopatic epilepsy; and 12 (44.5%) had cryptogenic epilepsy. Symptomatic epilepsy was due to the following causes: chronic vascular encephalopathy in 4 patients (n. 7, 8, 21, 23), dysembryoplastic neuroepithelial tumor in one patient (n. 1), arteriovenous malformation in one patient (n. 4), focal cortical dysplasia in one patient (n. 10), and poststroke encephalomalacia in one patient (n. 16). Secondarily generalized seizures (SGS) represented the 44.44%, partial complex seizures (PCS) the 40.74%, primarily generalized seizures (PGS) the 11.11%, and absence seizures the 3.74%.

Clinical and demographic characteristics of patients and the AEDs used are shown in Table 1.

3.1. Efficacy

The mean observation time was 5.8 months (range: 3.0–8.3 months). Overall, 23 out 27 patients (85.1%) were taking PER at the 3-months follow-up and 18 out 27 patients (67%) at the 6-months follow-up. At 3 months, 17 (62.9%) patients were responders, and 9 patients (33.3%) were seizure-free. At 6 months, of the 18 patients who continued the study, 16 (59.2%) were responders, and 6 (22.2%) were seizure-free (Table 2). We also compared seizure frequency at baseline with that after 3 and 6 months of treatment. Median seizure frequency showed a significant improvement in Friedman's test ($p = <0.05$) at both 3 and 6 months of treatment. Efficacy data and the median frequency of seizures with their significance are showed in Table 2.

3.2. Tolerability

During treatment with PER, 18 out of the 27 patients (67%) experienced adverse drug-related events (AEs). The most common were related to the central nervous system: vertigo, ataxia, irritability, and aggression. Six out of 27 patients (22.2%) dropped out because of AEs: 2 because of vertigo, 2 because of ataxia, and 2 because of suicidal thoughts (one had a diagnosis of obsessive disorder at baseline). Ten out 27 (37%) patients developed AEs in the psychiatric domain. Of the six patients who already had a psychiatric disorder in comorbidity, two developed additional symptoms (patients n. 3 and n. 16).

Table 3
Characteristics of adverse events per patient and AED dose.

Patient	Adverse event	AED & PER	Regression	Time of onset (months)	Cause of drop	Comorbidity
1	Aggression	ZNS 300 + PER 6 mg	Regressed	2		None
2	Vertigo	LEV 2500 + PER 6 mg	Regressed	2		Rheumatoid arthritis
3	Psychotic decompensation	CBZ 800 + PER 8 mg		5		Psychotic dis. from medical condition (epilepsy)
4	Aggression – suicidal thoughts	OXA 1500 + PER 2 mg		6	Drop-6 months-suicidal thoughts	Hypertension
5	None	VPA 1500 + PER 4 mg				Personality disorder
6	None	LEV 1000 + PER 6 mg				Migraine- anxiety
7	Ataxia – night polyuria	LEV 2000 + PER 6 mg		6		Obesity
8	Vertigo	LEV 1000 + PER 2 mg		3	Drop-3 months- vertigo	Hypertension- cardiopathy
9	None	OXA 1200 + PER 4 mg				None
10	Anxiety	LEV 2000 + PER 4 mg		6		Migraine
11	Ataxia	LEV 1750 mg + PER 4 mg		2		Migraine-eclampsia
12	None	ZNS 500 + PER 4 mg	Regressed	4		Anxiety-depression
13	None	CBZ 800 + PER 4 mg				Hypertension–food allergy
14	Irritability	LEV 3000 + PER 10 mg	I	6		None
15	Vertigo	LCS 400 + PER 8 mg		6		Migraine
16	Aggression – suicidal thoughts (drop)	LEV 3000 + PER 4 mg		3	Drop-6 months-aggression -suicidal thoughts	Obsessive disorder
17	None	VPA 1500 + PER 8 mg				Migraine-seasonal allergy
18	Vertigo	TPM 100 + PER 4 mg	Regressed	2		Ulcerous rectocolitis-migraine-dysthyroidism
19	Irritability – vertigo	TPM 100 + PER 4 mg		3	Drop-6 months- vertigo	Migraine
20	Ataxia	LCS 350 + PER 4 mg			Drop-3 months- ataxia	Migraine
21	Aggression	OXA 1200 + PER 6 mg	'	2		Small mental retardation due to perinatal asphyxia
22	Ataxia	OXA 1600 + PER 2 mg		1	Drop-3 months- ataxia	Food allergy
23	None	LCS 300 + PER 4 mg				Trombophilia
24	None	LEV 1000 + PER 4 mg		6		None
25	None	VPA 1500 + PER 4 mg				None
26	Irritability-anxiety	OXA 1200 + PER 6 mg		3		Gastric bypass -hypercolesterolemia serious obesity
27	Irritability	VPA 1300 + PER 4 mg	Regressed	2		Posttraumatic dis. from stress in remission

ZNS: zonisamide; LEV: levetiracetam; CBZ: carbamazepine; OXA: oxcarbazepine; VPA: valproic acid; LCS: lacosamide; TPM: topiramate.

Table 4
Results from cognitive variables and QOL.

Variable	Baseline n = 27	3 months n = 23	6 months n = 18
Imm. recall of Rey	44.07 ± 1.91	45.17 ± 2.42	44.28 ± 2.80
Del. recall of Rey	9.70 ± 0.55	9.70 ± 0.59	10.22 ± 0.79
C.T.	4.19 ± 0.22	4.43 ± 0.23	4.28 ± 0.19
T.M.T. A	50.30 ± 4.48	47.87 ± 4.54	48.06 ± 4.95
T.M.T. B	151.00 ± 13.91	141.39 ± 14.62	140.44 ± 16.22
S.T. time	29.04 ± 1.66	30.35 ± 1.62	30.89 ± 1.86
S.T. errors	2.00 ± 0.41	2.04 ± 0.44	1.83 ± 0.45
C.P.M. 47	27.81 ± 0.98	27.87 ± 0.97	27.39 ± 1.23
F.A.B.	14.70 ± 0.50	14.83 ± 0.55	14.67 ± 0.66
S.V.F.	17.70 ± 0.76	17.14 ± 0.82	16.54 ± 1.09
P.V.F.	29.78 ± 2.06	29.26 ± 2.24	27.89 ± 2.55
F. Rey copy	30.30 ± 0.89	30.98 ± 0.76	30.11 ± 1.03
QOLie 31	57.22 ± 2.94	59.22 ± 3.17	61.94 ± 4.73

Imm. recall of Rey: immediate recall trial of 15 words of Rey; Del. recall of Rey: delayed recall of 15 words of Rey; C.T.: Corsi Block-Tapping Test; T.M.T. A: Trail Making Test part A; T.M.T. B: Trail Making Test part B; S.T. time: Stroop Test corrected by completion time; S.T. errors: Stroop Test corrected by number of errors; C.P.M. 47: Colored Progressive Matrices; F.A.B.: Frontal Assessment Battery; S.V.F.: Semantic Verbal Fluency; P.V.F.: Phonetic Verbal Fluency; F. Rey copy: copy of Complex Figure of Rey; QOLie 31: QOL in Epilepsy Inventory.

One patient (n. 3) experienced a psychotic decompensation of a condition that was already present at baseline. In this case, treatment with PER was continued, and antipsychotic therapy was adjusted. Details are shown in Table 3. On the contrary, 3 patients with psychiatric comorbidities (anxiety-depressive, anxiety, and personality disorders) did not have psychiatric adverse events during follow-up (patients n. 5, 6, and 12). Oxcarbazepine (OXA) was the baseline monotherapy in 3 patients with psychiatric AEs: 2 patients showed aggression (also suicidal thoughts) and one showed irritability and anxiety. None of these patients had a history of psychiatric disorders, and there was no clear correlation with the dosage of PER. Three more patients treated with LEV dosages between 2000 and 3000 mg/day presented anxiety and irritability. In the patient with psychotic comorbidity, the accentuation of delirium was observed after increasing PER from 6 to 8 mg/day (in add-on to carbamazepine [CBZ] 800 mg), requiring a different antipsychotic therapy. The improvement of the aggressive symptoms in a patient after reducing PER from 6 to 4 mg/day, and of the irritability in another patient in a spontaneous manner is worthy of note. Four patients with nonpsychiatric AEs dropped out: 2 because of ataxia and 2 because of vertigo. Of the 5 patients who had vertigo, two were on LEV treatment (dosage: 1000–3000 mg/day), two on topiramate (TPM) (dosage: 100 mg/day), and one on LCS (dosage: 400 mg/day); while for the ataxia, two were on LEV (dosage: 1750–2000 mg/day), one on LCS (dosage: 350 mg/day), and one on OXA (dosage: 1600 mg/day).

3.3. Effects on cognitive functions and QOL

Regarding the cognitive functions and QOL, no significant changes were found between the baseline evaluation and the follow-up evaluations at 3 and 6 months. Results are shown in Table 4. Overall QOL assessment scores improved over time, but they did not achieve statistical significance (*QOLie 31 overall score*: at baseline = 57.2 ± 2.9; at 3 months follow-up = 59.2 ± 3.1; at 6 months follow-up = 61.9 ± 4.7).

Similarly, there were no statistically significant differences between responders and nonresponders neither on neuropsychological results, nor on QOL. The results of the ANOVA analysis showed that cognitive variables and the QOL were not influenced by response to treatment. At 6 months of PER therapy, nonresponders' (n = 2) scores in memory–verbal tests significantly improved compared to the baseline assessment. Scores are summarized in Table 5.

In the sample stratification according to the different baseline therapies (ZNS [zonisamide], LEV, CBZ, OXA, VPA, LCS, TPM), only the QOL showed a significant ($p < 0.05$) variation in patients treated with LEV compared with those treated with OXA and LCS after 6 months of treatment. Results are graphically expressed in Fig. 1.

4. Discussion

Up to now, only 3 clinical studies have systematically evaluated the cognitive effects associated with PER treatment [11–13]. To our knowledge, this is the first study with the aim to evaluate PER cognitive effects as first add-on therapy. This study presents some potential limitations because of its retrospective nature and the limited sample size. However, its strengths are its close follow-up, the exhaustiveness of the array of neuropsychological tests, and the use of PER as first add-on therapy. The ambulatory naturalistic setting represents both a strength and a limitation of the study. Indeed, data collection in an outpatient setting, where the choice of the pharmacological regime is entirely based on physician decision, is representative of a real and common epileptic population.

In our sample, most patients presented SGS and complex partial seizures. Only a very limited number of patients presented PGS. The mean duration of disease was 13.7 years. Overall efficacy data showed a good therapeutic response at both 3 and 6 months: the 3-month responders were the 62.9% and the 6-month responders were the 59.2%, suggesting the therapeutic efficacy of PER in generalized crises and focal crises with secondary generalization. This finding is supported by a meta-analysis of randomized controlled trials of seven additional AEDs [26]. In this study, PER (together with LCS and TPM) achieved significantly higher response rates on SGS as compared to all other forms of seizures [26]. In our sample, seizure-free patients were 33.3% and 22.2%, respectively, at 3 and 6 months. These percentages are slightly higher than those of previous real-life studies [27], and may be explained by differences in baseline seizures, type of epilepsy, duration and type of previous

Table 5
Analysis of cognitive variables and QOL in responders and nonresponders.

	Variable	Baseline	3 months	6 months
		Mean and standard deviation		
Imm. recall of Rey	Nonresponder	45.18 ± 2.86	48.71 ± 4.31	54.50 ± 1.50*
	Responder	43.31 ± 2.61	43.63 ± 2.92	43.00 ± 3.01
Del. recall of Rey	Nonresponder	9.09 ± 0.88	10.00 ± 0.92	12.00 ± 2.00
	Responder	10.13 ± 0.70	9.56 ± 0.71	10.00 ± 0.86
C.T.	Nonresponder	4.00 ± 0.38	4.29 ± 0.34	4.50 ± 0.50
	Responder	4.31 ± 0.27	4.50 ± 0.27	4.25 ± 0.21
T.M.T. A	Nonresponder	51.18 ± 6.72	42.29 ± 2.45	47.00 ± 6.00
	Responder	49.69 ± 6.17	50.31 ± 6.36	48.19 ± 5.56
T.M.T. B	Nonresponder	148.55 ± 18.61	122.43 ± 14.70	105.50 ± 22.50
	Responder	152.69 ± 20.18	149.69 ± 19.40	144.81 ± 17.89
S.T. time	Nonresponder	27.82 ± 2.73	27.57 ± 2.58	24.50 ± 1.50
	Responder	29.88 ± 2.13	31.56 ± 1.83	31.69 ± 2.01
S.T. errors	Nonresponder	1.91 ± 0.62	1.29 ± 0.42	1.00 ± 0.00*
	Responder	2.06 ± 0.57	2.38 ± 0.58	1.94 ± 0.50
C.P.M. 47	Nonresponder	27.64 ± 1.25	27.86 ± 0.88	26.50 ± 4.50
	Responder	27.94 ± 1.44	27.88 ± 1.34	27.50 ± 1.33
F.A.B	Nonresponder	15.27 ± 0.52	15.86 ± 0.21	16.00 ± 0.00*
	Responder	14.31 ± 0.76	14.38 ± 0.76	14.50 ± 0.73
S.V.F	Nonresponder	18.43 ± 1.35	18.57 ± 1.03	17.25 ± 4.75
	Responder	17.20 ± 0.91	16.52 ± 1.02	16.45 ± 1.15
P.V.F	Nonresponder	31.45 ± 2.79	31.57 ± 2.85	29.00 ± 1.00
	Responder	28.63 ± 2.94	28.25 ± 2.84	27.75 ± 2.88
F. Rey copy	Nonresponder	30.68 ± 1.51	31.42 ± 1.00	30.50 ± 0.50
	Responder	30.03 ± 1.13	30.81 ± 0.96	30.06 ± 1.16
QOLie 31	Nonresponder	55.00 ± 5.54	55.29 ± 4.60	70.50 ± 12.50
	Responder	58.75 ± 3.29	60.94 ± 3.83	60.88 ± 5.15

Data are analyzed "per protocol", so dropouts were not included in the analysis.
n. of patients tested before PER administration: 27.
n. of patients tested at the 3 months follow-up: 23 (n. 17 responders, n. 6 nonresponders).
n. of patients tested at the 6 months follow-up: 18 (n. 16 responders, n. 2 nonresponders).
* Significant on Student's *t*-test for couple data with a $p < 0.05$ vs baseline.

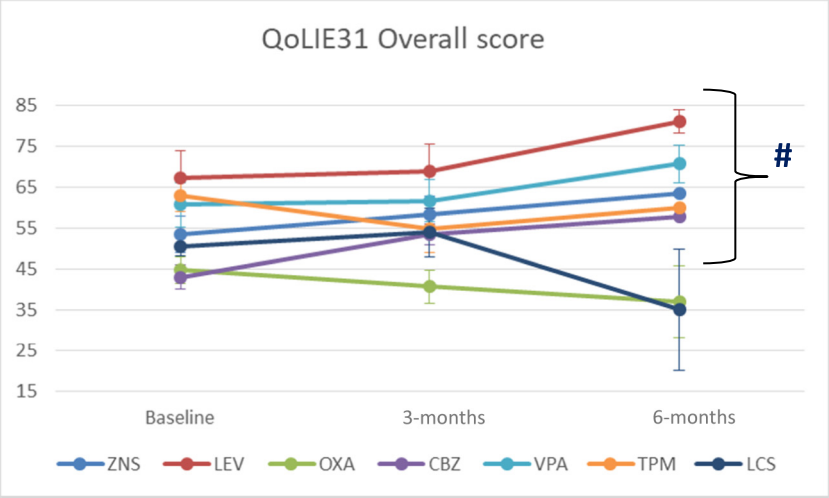

Fig. 1. # = Significant on ANOVA analysis with a $p < 0.05$. ZNS: n. 2 pts; LEV: n. 9 pts; CBZ: n. 2 pts; OXA: n. 5 pts; VPA: n. 4 pts; LCS: n. 3 pts; TPM: n. 2 pts.

treatments, differences in study methodologies, PER titration, concomitant AEDs, and number of concomitant AEDs. As a matter of fact, enzyme inducers can interfere with PER metabolism and reduce its serum concentrations [28]. In phase III studies, 3 enzyme inducers (CBZ, OXA, and phenytoin) increased PER clearance, reducing serum levels by up to 30% [29,30]. In our sample, antiepileptic monotherapy at baseline was predominantly composed of LEV followed by OXA and VPA. From our data, it is not possible to draw conclusions on the best association with PER in terms of therapeutic efficacy, because of the small sample size and of the heterogeneous representation of AEDs. However, in the group of patients treated with LEV, there is a high percentage of seizure-free patients at both 3- and 6-months follow-up.

Adverse events were found in the 66.6% of patients and, as in previous studies [31], most of them were related to the central nervous system. Only 6 patients (22.2%) dropped out because of AEs.

These percentages are higher as compared to the randomized placebo-controlled trial results [32], being more similar to those of real-life studies [30,33–35]. Indeed, our data are in line with other real-life studies that consider baseline psychiatric comorbidities as predictive of psychiatric AEs [34].

In randomized controlled trials with PER [30], a dose-dependent increase in hostility and aggression was found. Such findings have been observed also in two patients of our study. In our sample, OXA was the most common baseline monotherapy associated with aggression, irritability, and anxiety, but the sample size is too small to draw conclusions about it. Levetiracetam was the antiepileptic treatment most frequently associated with vertigo and ataxia.

Regarding cognitive functions and QOL, no significant changes were found between baseline and 3 and/or 6 months of treatment. No statistically significant differences in neuropsychological results or QOL were found between responders and nonresponders either. In addition, a stratified antiepileptic analysis used at baseline showed that QOL in patients taking LEV was significantly higher than those treated with OXA and LCS. Although this has not been analyzed for cognitive parameters, it seems that the association with LEV in our sample suggests a better QOL as compared to treatment with OXA and LCS. Although the sample size is too small to evaluate statistically significant differences between groups, we considered such data particularly interesting and, in our opinion, worthy of further investigation.

5. Conclusion

The results of this retrospective study suggest that short-term treatment with PER does not interfere with cognitive functions and QOL, which is also supported by other published real-life studies [12,13]. Furthermore, efficacy data showed a good therapeutic response with a significant improvement in seizure control. These results need to be further studied in longitudinal studies and larger patients' samples.

Acknowledgments

Dr. Mauro Pagliuca received a financial support from EISAI.

Declaration of Competing Interests

The other authors have no conflict of interest or financial disclosures.

References

[1] Kerr MP. The impact of epilepsy on patients' lives. Acta Neurol Scand Suppl 2012; 194:1–9.
[2] Meador KJ. Cognitive and memory effects of the new antiepileptic drugs. Epilepsy Res 2006;68:637.
[3] Mula M, Trimble MR. Antiepileptic drug-induced cognitive adverse effects: potential mechanisms and contributingfactors. Send to CNS Drugs 2009;23(2):121–37.
[4] Mula M. Recent and future antiepilepticdrugs and their impact on cognition: what can we expect? Expert Rev Neurother 2012;12(6):667–71.
[5] Cochrane HC, Marson AG, Baker GA, Chadwick DW. Neuropsychologicaloutcomes in randomizedcontrolled trials of antiepilepticdrugs: a systematicreview of methodology and reporting standards. Epilepsia 1998;39(10):1088–97.
[6] Baker GA, Marson AG. Cognitive and behavioural assessments in clinical trials: what type of measure? Epilepsy Res 2001;45(1–3):163–7.
[7] Witt JA, Helmstaedter C. Monitoring the cognitive effects of antiepilepticpharmacotherapy–approaching the individual patient. Epilepsy Behav 2013;26(3):450–6.
[8] French JA, Krauss GL, Biton V, Squillacote D, Yang H, Laurenza A, et al. Adjunctive perampanel for refractory partial-onset seizures: randomized phase III study 304. Neurology 2012;79(6):589–96.
[9] French JA, Krauss GL, Steinhoff BJ, Squillacote D, Yang H, Kumar D, et al. Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: results of randomized global phase III study 305. Epilepsia 2013;54(1):117–25.
[10] Krauss GL, Serratosa JM, Villanueva V, Endziniene M, Hong Z, French J, et al. Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures. Neurology 2012;78(5):1408–15.
[11] Meador KJ, Yang H, Piña-Garza JE, Laurenza A, Kumar D, Wesnes KA. Cognitive effects of adjunctive perampanel for partial-onset seizures: a randomized trial. Epilepsia 2016;57(2):243–51.
[12] Piña-Garza JE, Lagae L, Villanueva V, Renfroe JB, Laurenza A, Williams B, et al. Long-term effects of adjunctive perampanel on cognition in adolescents with partial seizures. Epilepsy Behav 2018;83:50–8.
[13] Meschede C, Witt JA, Rademacher M, von Wrede RD, Elger CE, Helmstaedter C. Evaluating the longer-term cognitive effects of adjunctive perampanel compared to lacosamide in a naturalistic outpatient setting. Seizure 2018;58: 141–6.
[14] Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 1989;30:389–99.

[15] Baker GA, Jacoby A, Buck D, Stalgis C, Monnet D. Quality of life of people with epilepsy: a European study. Epilepsia 1997;38:353–62.
[16] Caltaginore C, Gainotti G, Carlesino GA, Parnetti L. Batteria per la valutazione del detioramento mentale (parte I): descrizione di uno strumento di diagnosi neuropsicologica. Arch Psicol Neurol Psichiatr 1995;56(4):461–70.
[17] Mammarella IC, Tolso C, Pazzaglia F, Cornoldi C. BVS-Corsi. Batteria per la valutazione della memoria visiva. Edizioni Erikson; 2008.
[18] Caffarra P, Vezzadini G, Dieci F, Zonato A, Venneri A. Una versione abbreviata del test di Stroop:dati normativi nella popolazione Italiana. Nuova Riv Neurol 2002;12(4):111–5.
[19] Giovagnoli AR, Del Pesce M, Mascheroni S, Simoncelli M, Laiacona M, Capitani E. Trail Making Test: normative values from 287 normal adult controls. Ital J Neurol Sci 1996;17(4):305–9.
[20] Apollonio I, Leone M, Isella V, Piamarta F, Consoli T, Villa ML, et al. The Frontal Assessment Battery (FAB): normative values in an Italian population sample. Neurol Sci 2005;26(2):108–16.
[21] Spinnler H, Tognoni G. Standardizzazione e Taratura Italiana di Test Neuropsicologici. Ital J Neurol Sci 1987;6(8):81–3.
[22] Caffarra P, Vezzadini G, Dieci F, Zonato A, Venneri A. Rey-Osterrieth Complex Figure: normative values in an Italian population sample. Neurol Sci 2002;22:443–7.
[23] Basso A, Capitani E, Laicona M. Raven's Coloured Progressive Matrices: normative values on 305 adult normal controls. Funct Neurol 1987;2:189–94.
[24] Beghi E, Niero M, Roncolato M. Validity and reliability of the Italian version of the Quality-of-Life in Epilepsy Inventory (QOLIE-31). Seizure 2005;14(7):452–8.
[25] López-Góngora M, Martínez-Domeño A, García C, Escartín A. Effect of levetiracetam on cognitive functions and quality of life: a one-year follow-up study. Epileptic Disord 2008;10(4):297–305.
[26] Hemery C, Ryvlin P, Rheims S. Prevention of generalized tonic-clonic seizures in refractory focal epilepsy: a meta-analysis. Epilepsia 2014;55:1789–99.
[27] Tsai JJ, Wu T, Leung H, Desudchit T, Tiamkao S, Lim KS, et al. Perampanel, an AMPA receptor antagonist: from clinical research to practice in clinical settings. Acta Neurol Scand 2018;137(4):378–91.
[28] Steinhoff B, Ben-Menachem E, Ryvlin P, Shorvon S, Kramer L, Satlin A, et al. Efficacy and safety of adjunctive perampanel for the treatment of refractory partial seizures: a pooled analysis of three phase III studies. Epilepsia 2013; 54:1481–9.
[29] Laurenza A, Ferry J, Hussein Z. Population pharamacokinetics and pharmacodynamics of perampanel: a pooled analysis of three phase III trials. Epilepsy Curr 2012;12 (Suppl. 1):231.
Rheims S, Ryvlin P. Profile of perampanel and its potential in the treatment of partial onset seizures. Neuropsychiatr Dis Treat 2012;9:629–37.
[30] Ettinger AB, LoPresti A, Yang H, Williams B, Zhou S, Fain R, et al. Psychiatric and behavioral adverse events in randomized clinical studies of the non competitive AMPA receptor antagonist perampanel. Epilepsia 2015;56(8):1252–63.
[31] Rugg-Gunn F. Adverse effects and safety profile of perampanel: a review of pooled data. Epilepsia 2014;55(Suppl. 1):13–5.
[32] Juhl S, Rubboli G. Perampanel as add-on treatment in refractory focal epilepsy. The Dianalund experience. Acta Neurol Scand 2016;134:374–7.
[33] Shah E, Reuber M, Goulding P, Flynn C, Delanty N, Kemp S. Clinicalexperience with adjunctive perampanel in adultpatients with uncontrolled epilepsy: a UK and Ireland multicenter study. Seizure 2016;34:1–5.
[34] Villanueva V, Garcés M, López-González FJ, Rodriguez-Osorio X, Toledo M, Salas-Puig J, et al. Safety, efficacy and outcome-related factors of perampanel over 12 months in a real-world setting: the FYDATA study. Epilepsy Res 2016;126:201–10.
[35] Wehner T, Mannan S, Turaga S, Vallabhaneni K, Yip HM, Wiggans C, et al. Retention of perampanel in adults with pharmacoresistant epilepsy at a single tertiary care center. Epilepsy Behav 2017;73:106–10.