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Efficacy and tolerability of perampanel and levetiracetam as first add-on therapy in patients with epilepsy: A retrospective single center study

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ABSTRACT

Perampanel (PER) is a third generation antiepileptic drug (AED), recently approved as add-on therapy in both focal and generalized seizures. Levetiracetam (LEV) is a second generation AED, widely used in patients with epilepsy because of its favorable safety and efficacy profiles. Perampanel and LEV treatments have been associated with the occurrence of similar adverse events (AEs) (sleepiness, irritability, depression, anxiety, aggressiveness). The aim of the present retrospective single center study was to verify the efficacy and tolerability of PER and LEV used as first add-on therapy in patients with epilepsy affected by secondarily generalized seizures. We collected data from 15 patients treated with PER and 26 patients treated with LEV and followed at our site with follow-up visits at 3, 6, and 12 months. This retrospective study documented the comparable efficacy of PER and LEV as first add-on treatments in patients affected by uncontrolled secondarily generalized seizures. However, more patients withdrawn LEV because of AEs compared with PER at the 3- and 12-month follow-up visits. The better tolerability of PER observed in this study could be related to the low therapeutic dose of PER prescribed when it is used as first adjunctive treatment for better controlling secondarily generalized seizures.

1. Introduction

Epilepsy is a neurological condition affecting 1–2% of the global population across all ages [1–2]. Antiepileptic drugs (AEDs) significantly reduce seizure frequency in patients affected by epilepsy, although sometimes, and more frequently in focal epilepsies, a single AED cannot permit the complete resolution of seizures [3]. Thereafter, an adjunctive AED may allow obtaining seizure freedom.

Perampanel (PER) is a third-generation AED, recently licensed for the treatment of focal and generalized epilepsies [4–5]. It is a non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazole-proprionic acid (AMPA) receptor antagonist demonstrated efficacious in focal and generalized seizures in randomized controlled trials and clinical real-life studies [6–8]. Levetiracetam (LEV) is a second-generation AED widely used in patients with epilepsy in the last decade. It has a high therapeutic index and wide margin of safety compared with other AEDs [9]. Taking into account the literature describing the real-life use of the aforementioned AEDs, it is conceivable that PER and LEV may show a similar adverse event (AE) profile. Indeed, PER has been associated with irritability, asthenia, sedation, and aggressiveness, which have been mainly observed at high doses and in patients with intellectual disability [10–11]. Conversely, sleepiness and, less frequently, psychiatric AEs (PAEs: psychosis, depression, anxiety, somatization, obsessive-compulsiveness) and psychogenic nonepileptic seizures (PNES) have been related to LEV treatment in recent observational studies [12–16].

The aim of the present retrospective single center analysis was to compare the efficacy and tolerability of PER and LEV when used as first adjunctive therapy in a population of patients affected by uncontrolled secondarily generalized seizures.

2. Methods

The present report is a retrospective observational single center data collection based on individual chart reviews of patients affected by drug-resistant epilepsy [17], who started LEV or PER as first add-on AED for better controlling their secondarily generalized seizures from October 2015 to August 2016. Patients were classified according to the 1981 International League Against Epilepsy, which was in use when patients were diagnosed [18]. Since it is a common clinical practice at our Epilepsy Centre to fix visits before starting a new therapy and after 3, 6, and 12 months of treatment, we collected and analyzed data considering those time points [19]. The following data were analyzed: age, gender, time since epilepsy onset, etiology (symptomatic or cryptogenic epilepsy), history of psychiatric disorders, 1-month total seizure count at baseline and at 3, 6, and 12 months after starting LEV or PER,

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and AED history. Titration was performed according to clinical practice for PER and LEV. For the statistical analysis, we considered the following: i) 75% responder rate, defined as the percentage of patients obtaining a minimum of ≥75% seizure reduction in seizure frequency compared with baseline, ii) seizure freedom (considered as the absence of seizures between time points), iii) drug retention rate at 3, 6, and 12 months, iv) maintenance dose of LEV and PER at 3, 6, and 12 months, and v) the occurrence of AEs related to LEV or PER treatments causing the discontinuation of treatment at 3, 6, and 12 months.

The statistical analysis was performed using commercial software Statistica 10.0 program, Statsoft Inc., Tulsa, OK, USA [20]. Descriptive data were expressed as mean and standard deviation for quantitative analyses. For between-group comparisons of dichotomous variables, the Odds Ratio (OR) was calculated, and p value was set at $p < 0.05$ for statistical significance. The Student's *t* test was used to compare descriptive data. This retrospective observational study protocol was approved by the Independent Ethical Committee of the University Hospital of Rome "Tor Vergata".

3. Results

Forty-one patients affected by uncontrolled secondarily generalized seizures were included in this retrospective analysis. No patient was affected by learning or intellectual disabilities. Perampanel was administered as first add-on AED in 15 patients (8M, 7F, aged 18–79 years, Table 1), whereas LEV was proposed as the first add-on AED in 26 patients (12M, 14F, aged 19–82 years, Table 1). The two groups did not significantly differ in terms of demographic data; moreover, groups did not differ for seizure baseline frequency, disease duration, age of epilepsy onset, history of psychiatric disorders, and previous AEDs (Table 1). Eleven patients treated with PER and 19 patients treated with LEV showed an unremarkable brain MRI, and epilepsy was defined as cryptogenic; on the other hand, 4 PER patients and 7 LEV patients were affected by symptomatic epilepsy since they showed brain magnetic resonance imaging (MRI) alterations (description of brain MRI is reported in Table 1). Finally, 13 patients were previously treated by two monotherapies before starting a rationale polytherapy (8 in the LEV group and 5 in the PER group, respectively); the remaining patients were previously treated by a single monotherapy.

Analyzing data achieved at 3, 6, and 12 months, we documented the similar efficacy of PER and LEV, considering seizure freedom or seizure reduction ≥75% (Fig. 1). Notably, AEs leading to discontinuation of treatment were more frequent in LEV compared with PER group at 3 months (6/26 vs 0/15, $p < 0.05$, OR 5.16, Table 2 and Fig. 2) and 12 months (2/15 vs 9/26, $p < 0.01$, OR 3.44, Table 2 and Fig. 2). At 6 months, we did not find differences in AEs leading to discontinuation of treatment in patients treated by PER compared with LEV (1/15 vs 7/26, Table 2 and Fig. 2). Considering patients with previous history of psychiatric disorders, 1 of 2 patients who discontinued PER was affected by anxiety. On the other hand, 3 of 9 patients withdrawing LEV for AEs presented previous history of psychiatric disorders (depression).

4. Discussion

The present retrospective single center study investigated the efficacy and tolerability of PER and LEV as first adjunctive therapy in patients affected by uncontrolled secondarily generalized seizures. We documented the similar efficacy of PER and LEV in reducing the frequency of secondarily generalized seizures at 3, 6, and 12 months follow-up visits. Notably, at 3- and 12-month follow-ups, fewer patients treated with PER showed AEs than patients treated with LEV. Consistently, higher retention rates at 3 and 12 months were observed in patients treated with PER compared with LEV. This finding may result very impressive since LEV has been considered one of the most commonly used and safe AED in the last decade for treating both drug-naïve and drug-resistant patients with epilepsy [9]. However, several PAEs have been related to LEV treatment in the past years. In particular, psychosis, PNES, depression, anxiety, and aggressiveness have been described in patients with epilepsy treated with LEV [12,15–16]. In agreement with this observation, drug-related psychotic disorders have been recently associated not only with female sex and temporal lobe epilepsy, but also specifically with LEV treatment in patients with

Table 1
Demographic and clinical data of PER and LEV patients.

		PER (n = 15) Mean ± SD	LEV (n = 26) Mean ± SD	p value
Age (years)		40 ± 18.53	41.69 ± 17.87	NS
Gender		8M, 7F	12M, 14F	NS
Time since epilepsy onset (years)		15.13 ± 10.33	10.96 ± 5.25	NS
Etiology		11 cryptogenetic, 4 symptomatic: 2 microvascular lesions 1 posterior right temporal venous malformation 1 right temporoparietal vascular injury	19 cryptogenetic, 7 symptomatic: 4 microvascular lesions 1 left frontal venous malformation 1 right insular vascular injury 1 left temporal cortical dysplasia	NS
Nocturnal seizures		5/15	6/26	NS
History of psychiatric disorders		1/15 (anxiety)	4/26 (depression)	NS
Daily dosage (mg)	3 months	4.13 ± 0.51	1692.31 ± 401.92	NA
	6 months	5.27 ± 1.35	1777.78 ± 646.76	NA
	12 months	5.42 ± 2.51	1941.18 ± 788.24	NA
Number of previous AEDs		1.6 ± 0.51	1.31 ± 0.47	NS
Concomitant AEDs		6 CBZ 5 VPA 2 OXC 1 ZNS 1 PB	8 VPA 6 CBZ 5 PB 4 OXC 2 ZNS 1 PHT	NA
Baseline seizures/month		3.27 ± 2.22	3.3 ± 2.33	NS
Follow-up seizure reduction ≥75%	3 months	13/15	16/20	NS
	6 months	12/14	19/19	NS
	12 months	13/13	17/17	NS
Seizure-free	3 months	10/15	14/20	NS
	6 months	8/14	13/19	NS
	12 months	11/13	15/17	NS

Abbreviations: PER, perampanel; LEV, levetiracetam; AEDs, antiepileptic drugs; VPA; valproic acid; OXC, oxcarbazepine; CBZ, carbamazepine; PB, phenobarbital; ZNS, zonisamide; SD, standard deviation; NS, not significant; NA, not admitted.