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Effectiveness and safety of perampanel in adults with mesial temporal epilepsy

A single-center postmarketing study in Taiwan

Chih-Yin Lin, MD, Siew-Na Lim, MD, PhD, Hsing-I Chiangn, MD, Mei-Yun Cheng, MD, PhD, Chun-Wei Chang, MD, Wei-En Johnny Tseng, MD, Hsiang-Yao Hsieh, MD, Han-Tao Li, MD, Tony Wu, MD, PhD*

Abstract

Mesial temporal lobe epilepsy (MTLE) is a common epilepsy syndrome often refractory to antiepileptic drug (AED) treatment. The purpose of this study was to evaluate the effectiveness and tolerability of perampanel (PER) as add-on treatment for patients of MTLE.

We pooled retrospective data from adult patients with MTLE, from a tertiary center in Taiwan, who were prescribed PER between March 2016 and December 2016. The retention, responder, and seizure-free rate as well as the treatment emergent adverse events were assessed after 6 months of PER adjunctive treatment in this single-center postmarketing study.

Review of medical records revealed that adequate data were available for 44 patients who were being administered PER (mean age: 42.0±13.3 years, 24 females; baseline mean seizure frequency: 5.4 per 28 days). Twelve patients exhibited hippocampal sclerosis (HS). Open-label PER was added to ongoing medications. Twelve patients withdrew because of ineffectiveness (n=6) or adverse effects (n=6). The retention rate was 72.7% at 6 months. On final evaluation, with a mean PER dose of 5.7 mg/day for 6 months, a ≥50% reduction in seizure frequency was observed in 46.9% of the patients, and 5 patients became seizure-free. The effectiveness was similar for patients with or without HS. Twenty-three patients (52.3%) experienced adverse effects. The most common adverse effects were dizziness, ataxia, and irritability.

Our results suggest that PER, at doses of 2 to 12 mg/day, reduces seizure frequency effectively with acceptable safety profiles for adults with MTLE.

Keywords: adverse drug events, perampanel, temporal lobe epilepsy, treatment outcome

1. Introduction

Mesial temporal lobe epilepsy (MTLE) is the most common focal-onset epilepsy among adults. Patients of MTLE with hippocampal sclerosis (HS) respond poorly to antiepileptic drugs (AEDs), and surgically remediable.[1] However, some patients are not considered suitable for surgical intervention owing to multiple epileptic foci, difficulty in locating the foci, or nonconcordant electrophysiological and structural findings. Therefore, there is a need for the development or application of new AEDs for these difficult cases of MTLE.

Perampanel (PER) is a newly developed AED with a novel mechanism of action. It acts as a noncompetitive antagonist of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor on the postsynaptic neuron.[2] Three phase III double blind randomized clinical trials have demonstrated significant seizure reduction in partial onset seizures, with or without secondary generalization, and idiopathic generalized seizure.[3–5] The most common dose-related adverse events (AEs) are dizziness and somnolence.[6] Animal models and preclinical evaluation of PER and other noncompetitive AMPA receptor antagonists have suggested a promising effect against MTLE.[7] Krestel et al showed increasing levels of calcium-permeable AMPA receptors in the hippocampus rat models of seizure, thus, leading to circuit hyperexcitability and increased seizure susceptibility.[8] In patients with treatment-resistant TLE, AMPA receptor was found to be upregulated.[9] Based on this background, we undertook this real-world study in order to assess PER effectiveness and safety as add-on therapy in patients with MTLE.

2. Materials and methods

2.1. Patients

We retrospectively identified adult patients with MTLE who were administered PER as adjunctive therapy between March 2016

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Epilepsy Section, Department of Neurology, Chang Gung Memorial Hospital Linkou Medical Center and Chang Gung University College of Medicine, Taoyuan, Taiwan.

** Correspondence: Tony Wu, Epilepsy Section, Department of Neurology, Chang Gung Memorial Hospital Linkou Medical Center and Chang Gung University College of Medicine, 5, Fu-Hsin Street, Kwei-Shan, Taoyuan 333, Taiwan (e-mail: tonywu@cgmh.org.tw).*

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and December 2016 in the Department of Neurology and Pediatric Neurology in our hospital, using the hospital information system. All clinical files and instrumental records of patients were reviewed and analyzed under the approval of the local research ethics committee. Entry criteria were: patients aged ≥12 years; and a minimum of 6 months follow-up once the treatment with PER commenced. Wherever possible, the diagnosis of seizure types, and MTLE with or without HS, were confirmed via magnetic resonance imaging (MRI) imaging, based on the International League Against Epilepsy (ILAE) classification.[10] Patients who had poor compliance or clinic attendance, or had inaccurate or unreliable clinical records were excluded.

2.2. Data collection

The patient clinical characteristics at baseline included age, sex, family and personal medical histories, age at epilepsy onset, seizure types, epilepsy syndrome and etiology, seizure frequency, previous and concomitant AEDs, results of EEG, and MRI. For the purpose of analysis, concomitant AEDs were classified as enzyme-inducing AED (EIAED; carbamazepine, oxcarbazepine, and phenytoin) and non-EIAED (any other AED). Patients were described as taking EIAEDs if taking at least one EIAED. Diagnosis of HS was based on visual analysis of brain MRI in case of increased hippocampal signal on T2-weighted images, decreased signal on T1-weighted images, and hippocampal atrophy. Complete seizure frequency, AEs, the dose of PER, and titration scheme were recorded and conducted at every visit, for at least 6 months.

Effectiveness was assessed using descriptive analyses of responder rates, and seizure freedom was evaluated by comparing the frequency of seizures during the 4 weeks preceding the start of treatment with PER (baseline), and afterwards, at 6 months (average of last 3 months). Analysis of effectiveness outcomes included all patients who fulfilled the inclusion criteria, and received PER for the entire 6-month period. In addition, effectiveness outcomes were compared between groups of patients with or without HS. The safety was assessed for all 44 patients, who fulfilled the inclusion criteria, and had received at least one dose of PER. The occurrence of AEs, as defined according to Food and Drug Administration definitions (FDA, 2014), was obtained from the patients at each follow-up visit, and the relationship with PER administration was further considered by the attending physicians.

2.3. Statistical analysis

Inferential statistical tests were employed to describe the mean and standard deviation for the quantitative variables (with normal distribution), median (without normal distribution), and percentages for the qualitative variables. For between-group comparisons, the Chi-square test and one-way analysis of variance were used for the analysis of categorical variables, and *t* test was used for continuous variables and arithmetic means. The SPSS software version 21 (SPSS, Chicago, IL) was used to perform all the statistical analysis.

3. Results

3.1. Patient demographics and deposition

Data from 44 patients with pharmaco-resistant MTLE, who underwent treatment with PER as adjunctive therapy, were identified and included in the analysis (25 women; 19–67 years, mean: 42 ± 13.3 years). Complete data was available for all the patients for at least 6 months of follow-up after the initiation of PER treatment. Baseline demographic and clinical characteristics are summarized in Table 1. The mean age at onset of epilepsy was 20.1 ± 15.0 years, while mean duration of epilepsy was 21.9 ± 11.9 years.

Table 1

Baseline demographic and clinical characters (n = 44).

Category	N, % or mean ± SD
Female	24 (54.0%)
Mean age, y	42.0 ± 13.3
Age range, y	19–67
Onset age, y	20.1 ± 15.0
Duration of epilepsy, y	21.9 ± 11.9
Seizure type (seizure type classification, ILAE 1981)	
Focal onset motor seizure without impaired awareness	1 (2.3%)
Focal onset motor seizure with impaired awareness	9 (20.5%)
Focal onset motor seizure with impaired awareness to bilateral tonic-clonic seizure	34 (77.3%)
Seizure frequency at baseline, n per 28 d (max, min)	5.4 (70, 0.3)
Median seizure frequency, per 28 d	1.4
No. of previously tried AEDs	5.23 ± 2.30
No. of concomitant AEDs at baseline	
1	3 (6.8%)
2	18 (40.9%)
3	14 (31.8%)
4	7 (15.9%)
5	1 (2.3%)
6 or more	1 (2.3%)
Concomitant AEDs (most used)	31 (70.5%)
Levetiracetam	21 (47.7%)
Oxcarbazepine	18 (40.9%)
Valproate	16 (36.4%)
Topiramate	13 (29.5%)
Carbamazepine	11 (25.0%)
Lamotrigine	8 (18.2%)
Clobazam	6 (13.6%)
Zonisamide	4 (9.1%)
Pregabalin	3 (6.8%)
Phenytoin	2 (4.5%)
No. of concomitant enzyme inducing AED	31 (70.5%)
No. of concomitant nonenzyme inducing AED	13 (29.5%)
MRI finding	
HS	12 (27.3%)
No HS	32 (72.7%)

AED = antiepileptic drugs, HS = hippocampal sclerosis, MRI = magnetic resonance imaging, SD = standard deviation.

At the time when the PER treatment was initiated, all the patients were administered AEDs. The median of other concomitant AEDs, used in combined therapy along with PER, was 3. Other concomitant AEDs used in combination with PER included various combinations of oxcarbazepine, valproate, clobazam, levetiracetam, carbazepine, pregabalin, lacosamide, topiramate, lamotrigine, phenytoin, phenobarbital, vigabatrin, and gabapentin. Patients had previously failed an average of 5.23 ± 2.30 AEDs. Three patients had received deep brain stimulation for epilepsy before. The most frequently reported dominant seizure types were focal onset motor seizure with impaired awareness to bilateral tonic-clonic seizure (77.3%), followed by focal onset motor seizure with and without impaired awareness (20.5% and 2.3%, respectively).

3.2. Dosage distribution and efficacy

Add-on therapy with PER was usually initiated at 2 mg/day, administered before sleeping. The titration schedule was administered individually, but under the condition that PER was increased 2 mg/day every 2 weeks, up to 12 mg/day. The targeted doses varied, depending on clinical response and tolerability. Twelve patients (27%) failed to complete the 6-month period of PER treatment due to lack of effectiveness in 13.6% (6/44), and intolerable AEs in 13.6% (6/44) of the patients. Of the 32 patients who underwent at least 6 months of PER treatment (retention rate 72.7%), the mean dose of add-on PER was 5.56 mg (range 2–12 mg). Overall, most of the patients (n = 12; 37%) received 4 mg/day of PER as a maintenance dose, followed by 8 mg/day (n = 8; 25%), 2 mg/day (n = 5; 16%), 6 mg/day (n = 4; 13%), 10 mg/day (n = 2; 6%), and 12 mg/day (n = 1; 3%), respectively.

The PER treatment led to a significant reduction in seizure frequency. The global 50% responder rate was 46.9% (15 out of 32 patients completing the 6-month PER treatment), including complete seizure freedom in 5 (15.6%), and a reduction in seizure frequency from 99% to 75% in 6 patients (18.8%) (Fig. 1). No significant difference was observed between groups of patients with HS and without HS (Fig. 2). There were more patients on concomitant non-EIAED than patients on EIAEDs response to PER (38.5% vs 32.3%, respectively; $P = .755$) and achieved seizure free (15.4% vs 19.4%, respectively; $P = .692$), although not statistically significant neither.

3.3. Safety and tolerability

There were no PER-related severe AEs. The observed AEs occurred in 23 (52.3%) patients, who were treated with an average PER dose of 4.60 mg/day. The most frequently reported TEAE was dizziness (n = 11, 25.0%), followed by malaise (n = 4, 9.1%), irritability (n = 4, 6.8%), and ataxia (n = 3, 6.8%). The PER dosage was reduced for 9 (20.5%) patients, and discontinued for 6 (13.3%) due to AEs (dizziness in 2 patients; the remaining cases of discontinuation were associated with irritability, ataxia, and weight-gain). Although no previous history of psychiatric illness, psychiatric AEs were observed in 5 patients, 1 led to lowering of dosage, 1 led to discontinuation, and the remaining 3 resolved spontaneously. No severe psychiatric AEs, such as suicide ideation or aggression, were found. Interestingly, most of the patients experienced TEAEs were within 4 mg daily dose of PER after starting, suggesting that AEs were not correlated with the dosage.

4. Discussion

In this study, the 50% responder rate (46.9%) and seizure-free rate (15.6%) were slightly higher than previous randomized control trials on focal epilepsy, in which the 50% responder rates were 33.3% to 37.6%, and the seizure-free rates were 1.9% to 4.8%,[3–5] and similar to other postmarketing observations (50% responder rate 41.6%–57.5%, seizure-free rate 5%–27%).[11–15] Till date, no results regarding the effectiveness of PER in patients with MTLE have been reported. In previous studies on comparative AED effectiveness on patients with MTLE-HS, seizure freedom rates varied from 1.2% for gabapentin and vigabatrin to 11% for carbamazepine, with no clear advantage of newer over older AEDs.[16] Our result provides new information regarding the effectiveness of PER treatment for patients with MTLE, and suggests that PER might be a new promising choice for patients with MTLE.

Previous studies assessing the prognosis for seizure control showed that male sex, higher number of previously tried AEDs, and longer duration of epilepsy are associated with drug resistance.[17] A previous real-world study in Spain demonstrated that patients administered EIAEDs tend to require a higher dose of PER to achieve similar response to those not administered EIAEDs X. In this study, patients of MTLE with or without HS showed appreciable response to PER treatment. We had performed bivariate analyses to clarify whether any patient- or medication-related factors are associated with superior clinical responses. There was a lower number of concomitant AEDs used at baseline (although not statistically significant) in seizure-free and responder patients versus control group. Otherwise, there were no statistically significant differences in other parameters between seizure-free, responder, and control groups in our study, possibly due to the limited number of patients. Consistent with

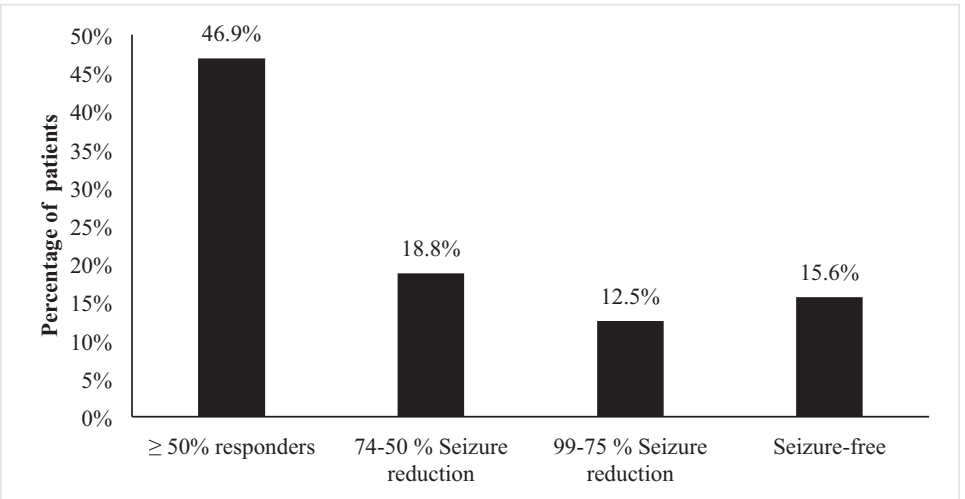

Figure 1. Seizure reduction rate after 6 months of perampanel therapy.

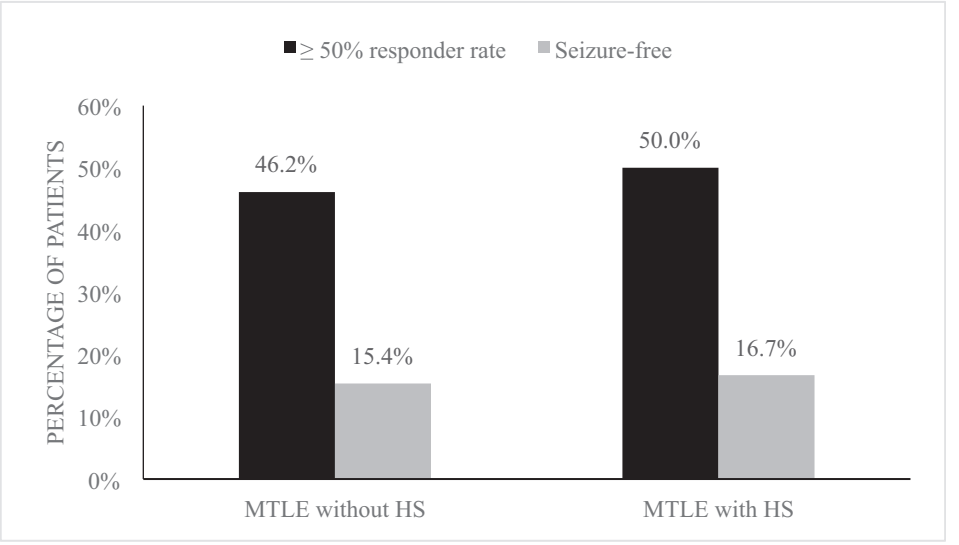

Figure 2. Fifty percent responder rate and seizure freedom in patients of MTLE with or without HS after 6 months of perampanel therapy ($P = .86$ and .94, respectively). HS = hippocampal sclerosis, MTLE = mesial temporal lobe epilepsy.

previous studies, higher dose of parempanel was required in responders with concomitant EIAEDs compared to those with non-EIAEDs (4.00 vs 3.60 mg, respectively, $P = .547$). Further studies are necessary to determine the predictors associated with a favorable clinical response or related dose management.

The AEs occurred in 52.3% of the patients; the result is similar to those of other studies (48%–89%[3–5] in randomized controlled trials, and 45%–67% in postmarketing studies).[11–14] The most common AEs in our patients receiving PER was dizziness, as observed in previous studies.[6,13] With respect to patients discontinuing PER due to intolerable AEs, our results are concordant with those of previous studies, in which discontinuation of PER treatment mostly occurs in 1 to 2 months, often due to TEAEs such as dizziness, somnolence, and ataxia.[15] Concerns regarding psychiatric and cognitive AEs are warranted, considering that various AEDs have been implicated in the development or worsening of behavioral and/or psychiatric symptoms.[18] Although there was no direct comparison between PER and other AEDs, overall psychiatric AEs were observed in 17.2% to 22.4% of the patients in trials,[5] and 29.3% to 30% patients in postmarketing studies.[11,15] Although the majority were of mild or moderate intensity, serious psychiatric AEs such as aggression, hostility, irritability, anger, and suicide ideation were reported in patients administered PER, especially those with higher PER dosage, rapid titration, and with prior personal or family history of psychiatric illness.[6,19] However, no serious psychiatric AEs were observed in our study. These might be due to lack of psychiatric illnesses in our patient group, and the use of a lower dose. Several studies have suggested a positive correlation between dose and AEs, but no such correlation was observed in our study. This might be due to a relatively lower proportion of the high PER dosage group in our study (34% of 8–12 mg) compared to other real-world data (48.6% of 8–12 mg in Spain). The lower dose distribution might be related to the relatively short duration of follow-up (6 vs 12 months in most other postmarketing studies) or the lower dosage in a Taiwanese study.[20] In addition to the effect of PER, MTLE showed association with behavioral/psychiatric comorbidity. Studies demonstrated that patients with MTLE presented a higher propensity to develop psychiatric disorders and dysfunction of several cognitive functions, due to the essential role of the limbic system in regulating emotions, mood, and behavior.[21,22] Careful monitoring of psychiatric and behavioral AEs, and slower titration, is essential, especially for those with history of psychiatric comorbidity.

Our study has some limitations, including the retrospective data collection from a relatively small number of patients and limited observation period. Further, we had variable clinic-visiting interval, dose-titrating schedule, and PER dosage in our patient group. Thus, the relationship between dose and effectiveness/AEs is not clear. Meanwhile, the exact treatment response of patients with relapsing-remission pattern could not be reflected. Since this is an open-label study, the placebo effects cannot be ruled out. Further extensive studies on a larger number of patients and a longer period of observation are needed for validation.

5. Conclusion

This retrospective study provides new and important clinical information on the effectiveness and tolerability of PER in the treatment of MTLE. Our results indicate that adjunctive PER treatment helps achieve clinically significant improvement, or even seizure freedom, in more than one-third of the patients of MTLE with and without HS.

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Author contributions

Data curation: Wu tony, Siew-Na Lim, Hsing-I Chiang, Mei-Yun Cheng, Chun-Wei Chang, Wei-En Johnny Tseng, Hsiang-Yao Hsieh, Han-Tao Li.
Formal analysis: Chih-Yin Lin, Wu tony.

Software: Chih-Yin Lin.
Supervision: Wu tony, Siew-Na Lim, Hsing-I Chiang, Mei-Yun Cheng, Chun-Wei Chang, Wei-En Johnny Tseng, Hsiang-Yao Hsieh, Han-Tao Li.
Validation: Wu tony, Siew-Na Lim, Hsing-I Chiang.
Visualization: Wu tony.
Writing – original draft: Chih-Yin Lin.
Writing – review & editing: Wu tony.

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