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Evaluation of real-world effectiveness of perampanel in Japanese adults and older adults with epilepsy

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ABSTRACT

Objective. While previous studies have demonstrated the safety and effectiveness of perampanel (PER) in combination with other anti-seizure medications in adult patients, data for older patients are limited. This study aimed to confirm real-world safety and effectiveness of combination treatment with PER in Japanese patients with focal seizures with or without focal to bilateral tonic-clonic seizures (FBTCS) or generalised tonic-clonic seizures (GTCS) according to age subgroups (<65 and ≥65 years of age).

Methods. This large-sample prospective post-marketing observational study included a 24-52-week observation period after the first PER treatment. Safety was assessed according to adverse drug reactions (ADRs) and efficacy was evaluated based on the 50% responder rate and rates of overall symptom improvement.

Results. Among the 3,808 patients who were enrolled, 3,716 (3,026 patients aged <65 years and 690 patients aged ≥65 years) and 3,272 were included in the safety and efficacy analysis datasets, respectively. ADRs were reported for 1,247 patients (33.6%) in the safety analysis dataset. Of these, 36.2% and 22.2% were aged <65 years and ≥65 years, respectively, and the most common ADRs were somnolence (11.6%, 5.5%) and dizziness (9.7%, 5.4%). The 50% responder rates in patients aged <65 years and those ≥65 years were 60.1% and 89.0% for those with focal aware seizures (FAS) with motor signs; 48.0% and 60.0% for FAS without motor signs; 47.4% and 80.2% for focal impaired awareness seizures; 70.8% and 93.4% for FBTCS; and 63.6% and 88.9% for GTCS, respectively. The improvement rates of symptoms/conditions were also higher in patients aged ≥65 years than those <65 years.

Significance. PER was effective in reducing seizure frequency and was safe, especially in older patients. PER may be a clinical treatment option for older patients with seizure disorders.

Key words: perampanel, aged epilepsy patients, Japan, safety, effectiveness

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Starting at approximately 65 years, the incidence of epilepsy is known to increase with age [1]. In older patients, pharmaceutical tolerability is important because of an increased risk of age-related complications. Epilepsy in older adults is characterised by a high recurrence rate (66%-90% after the first seizure) [2] and a fatality rate that is two to three times higher than that in younger patients [3-5]. However, seizures can be easily suppressed using appropriate drugs [6]. Thus, adequate drug selection is important. Perampanel (PER) is a selective, non-competitive inhibitor of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

(AMPA) glutamate receptors (AMPA receptors) and suppresses excessive glutamate-mediated neuronal excitation [7-11]. Some Phase 3 studies have demonstrated the efficacy and safety of PER monotherapy or PER in combination with other therapeutics for treating patients with refractory focal seizures (FS) [12-16]. However, few studies have examined the use of PER in elderly patients with refractory FS. Further, subgroup analyses of data from elderly patients in three Phase 3 studies found that sample populations were insufficient (*e.g.*, 28 in one study) for statistical analyses [17].

We conducted a large-scale prospective post-marketing observational study (with primary data collection) to confirm the clinical safety and effectiveness of long-term treatment with PER in Japanese patients, 18 years of age or older, with FS with or without focal to bilateral tonic-clonic seizures (FBTCS) or generalised tonic-clonic seizure (GTCS). To address the lack of evidence regarding the long-term safety of PER in patients 65 years of age and older, both in Japan and globally, we performed a subgroup analysis of data from the sample population.

Materials and methods

Study design

Patients treated with PER in Japan were prospectively enrolled in this post-marketing observational study (with primary data collection) in accordance with the Good Post-marketing Study Practice (GPSP) Ordinance (NCT03059329).

According to the packaging instructions in Japanese, the usual oral dosage of PER for patients 12 years of age or older is initially 2 mg once daily at bedtime; the daily dose may then be increased by 2 mg at intervals of one week or longer. The maintenance dose of PER is 4-8 mg once daily in the absence of concomitant anti-seizure medications that accelerate the metabolism of this product, or 8-12 mg once daily in the presence of such concomitant drugs. As PER monotherapy had not yet been approved in Japan at the start of this study, the efficacy and safety of PER were evaluated in the context of combination therapy. The observation period comprised 52 weeks after the first treatment. If treatment was withdrawn during the observation period, the follow-up period comprised the four weeks after withdrawal. We terminated the study when the number of participants who had completed the 52-week observation period reached 300. At that point, for patients who had completed less than 52 weeks of observation, we analysed data from the first 24 weeks only. We used the last observation carried forward (LOCF) approach and included the data collected at the last efficacy assessment during the observation period. To reflect real-world clinical practice, we did not restrict changes in the doses of concomitant anti-seizure medications or addition of new medications to the treatment regimen.

Patients

Eligible participants were individuals aged 18 years or older who had FS with or without FBTCS or GTCS according to the 2017 International League Against Epilepsy Classification of Epileptic Seizures. Enrolment began on August 1st, 2016. The exclusion criterion was a history of PER administration. The patients were registered using a central registration system that involved the Electronic Data Capture system. Since the GPSP Ordinance does not require patient consent, it was not mandatory for this study.

Outcome measures

Data regarding sex, age, epilepsy classification, disease duration, and comorbid conditions were collected as patient background information. To determine the status of PER use, we collected data regarding the daily dose, administration period, and reasons for withdrawal. We assessed the retention rates at 52 weeks for all patients included in the safety analysis dataset, patients younger than 65 years, and patients 65 years of age or older.

Using MedDRA version 23.0, we assessed safety by monitoring adverse events (AEs) for which a causal relationship with PER could not be ruled out during the observation period. Current seizures and seizure-related events (*e.g.* abnormal electroencephalography, computed tomography, or magnetic resonance imaging findings and falls due to seizures) were not considered AEs.

We assessed the efficacy of PER by comparing the seizure frequency during the four weeks immediately prior to the last observation with the frequency during the four weeks before the start of PER use (baseline). We calculated the 50% responder rate (the percentage of patients who achieved a 50% or greater reduction in seizure frequency during the four weeks prior to the last observation), 100% responder rate (the percentage of patients who achieved seizure-free status during the four weeks prior to the last observation), and the median percent reduction in seizure frequency from baseline for focal aware seizures (FAS) with motor signs, FAS without motor signs, focal impaired awareness seizures (FIAS), FBTCS, and GTCS. We also assessed the rate of improvement in symptoms/conditions at 12, 24, and 52 weeks after PER administration. The investigator subjectively assessed improvement regarding seizure severity, seizure

duration, daily activities, and overall conditions (including frequency and intensity of seizures, AEs, and daily living status) on a scale from 1 to 7 (with an additional option for not evaluable) compared with the pre-treatment status.

Statistical analysis

The PER retention rate was estimated using the Kaplan-Meier method. To investigate factors that could potentially affect safety, we calculated and compared the incidences of adverse drug reactions (ADRs) in terms of patient background. We used multivariable logistic regression analysis to investigate the relationships between the incidence of ADRs and the above-mentioned factors.

We calculated the 50% and 100% responder rates for each type of seizure (the patients without a specific type of seizure at baseline were excluded from the respective analyses). Of the seven levels of general improvement, cases that were markedly improved, much improved, or slightly improved were considered "improved" and underwent improvement rate analyses. The improvement rate, defined as the percentage of patients who were considered "improved" was calculated with the number of "improved" patients as the numerator and the number of patients in the efficacy analysis set (minus non-evaluable patients) as the denominator. To investigate the factors that could affect efficacy, we calculated the percentage change in seizure frequency according to patient background and the efficacy rate in terms of overall symptom improvement. We then investigated the relationships between these rates and factors using appropriate analysis methods, including the chi-square test and logistic regression analysis. All tests were two-sided with a significance level of less than 5%. Data are shown as mean values with standard deviations (SD) or the median percent change (min, max). Statistical analyses were conducted using SAS, version 9.4.

We set the target sample size to 3,750 patients because 3,000 patients were required to detect at least one AE with a frequency of 0.1% and a 95% confidence interval. Assuming that the withdrawal rate within the 24-week observation period would be 20%, we planned to collect data from 3,750 patients to ensure that approximately 3,000 patients would complete the 24-week observation period.

Results

Participant demographics

Between August 1st, 2016, and March 31st, 2019, 3,808 patients were enrolled. Of these, 2,849 patients had an observation period of up to 52 weeks and 959 patients had an observation period of up to 24 weeks. We obtained evaluable data from 3,769 patients at the beginning of the assessment period (baseline) (*supplementary figure 1*). Among the 3,769 patients for whom we collected a case report form, 53 patients, including 28 patients who did not complete any assessments following the first treatment dose, were excluded from the evaluable dataset. Thus, the safety analysis dataset included 3,716 patients. A total of 444 patients, including 284 patients with other seizure types/no concomitant anti-seizure medications and 196 patients who were not assessed for seizure frequency or overall symptom improvement after the start of drug administration, were excluded from the efficacy dataset. Thus, the efficacy analysis dataset included 3,272 patients.

Table 1 shows the characteristics of the 3,716 patients included in the safety analysis dataset. Patients 65 years of age and older accounted for 18.6% of the sample. The disease duration was 10 years or longer for 65.5% of the sample. A substantially lower proportion of patients aged ≥65 years compared to those aged <65 years had a disease duration of 10 years or longer (25.9% vs.74.6%). During the 28 days prior to initiating PER, the proportions of patients younger than 65 years who experienced FS with or without FBTCS and GTCS were 69.3% and 13.0%, respectively, while those of patients aged 65 years or older were 61.0% and 4.8%, respectively. Seizures were not reported or were unknown during the 28 days of baseline in 16.0% of patients younger than 65 years of age and in 34.8% of patients 65 years of age or older; of these, 61.6% (298/484) and 44.6% (107/240) had clearly documented seizures within the 11 months prior to baseline, respectively.

In terms of aetiology, the proportions of cerebrovascular disorder, brain tumour, trauma, and degenerative disorders were higher in patients 65 years of age and older compared with patients younger than 65 years. Patients who were 65 years of age or older were also more likely to be taking one concomitant anti-seizure medication compared with the patients younger than 65 years. In addition, as shown in *supplementary table 1*, in most patients, there was no change in the number of concomitant anti-seizure medications at the last observation point (or at the end of treatment in patients who discontinued the study) compared with baseline.

PER dose and retention rate

The mean ± SD daily doses of PER in all patients (3,716 patients), patients younger than 65 years (3,026 patients), and patients 65 years of age or older (690 patients) were 3.7 ± 1.9 mg/d, 3.8 ± 2.0 mg/d, and 3.0

▼ **Table 1.** Baseline patient characteristics.

	All *n* = 3,716	Age <65 years *n* = 3,026	Age ≥65 years *n* = 690
Male	1,965 (52.9)	1,604 (53.0)	361 (52.3)
Female	1,751 (47.1)	1,422 (47.0)	329 (47.7)
Age (years), mean ± SD	45.0 ± 19.0 (*n* = 3,716)	37.9 ± 12.6 (*n* = 3,026)	76.0 ± 7.9 (*n* = 690)
Body weight (kg)	57.9 ± 15.5 (*n* = 2,452)	59.1 ± 16.2 (*n* = 1,924)	53.4 ± 11.5 (*n* = 528)
BMI (kg/m^2)			
<18.5	450 (12.1)	345 (11.4)	105 (15.2)
≥18.5 to <25	1,220 (32.8)	932 (30.8)	288 (41.7)
≥25	568 (15.3)	459 (15.2)	109 (15.8)
Unknown	1,478 (39.8)	1,290 (42.6)	188 (27.2)
Seizure type at baseline[a]			
FS with or without FBTCS[b]	2,517 (67.7)	2,096 (69.3)	421 (61.0)
GTCS[b]	426 (11.5)	393 (13.0)	33 (4.8)
Other seizure types	117 (3.1)	111 (3.7)	6 (0.9)
No seizure reported or Unknown	724 (19.5)	484 (16.0)	240 (34.8)
Epilepsy classification			
Genetic[b]	661 (17.8)	559 (18.5)	102 (14.8)
Structural[b]	2,734 (73.6)	2,227 (73.6)	507 (73.5)
Other, unknown[b]	321 (8.6)	240 (7.9)	81 (11.7)
Aetiology			
Genetic disease[b]	144 (3.9)	140 (4.6)	4 (0.6)
Neurodevelopmental malformation[b]	284 (7.6)	277 (9.2)	7 (1.0)
Perinatal events[b]	119 (3.2)	117 (3.9)	2 (0.3)
Trauma[b]	186 (5.0)	117 (3.9)	69 (10.0)
Brain tumour[b]	272 (7.3)	185 (6.1)	87 (12.6)
Cerebrovascular disorder[b]	402 (10.8)	181 (6.0)	221 (32.0)
Degenerative disorder[b]	69 (1.9)	31 (1.0)	38 (5.5)
Brain infection[b]	241 (6.5)	224 (7.4)	17 (2.5)
Immunological disease[b]	53 (1.4)	49 (1.6)	4 (0.6)
Other[b]	109 (2.9)	98 (3.2)	11 (1.6)
Unknown[b]	1,904 (51.2)	1,657 (54.8)	247 (35.8)
Disease duration (years)			
<10	1,173 (31.6)	733 (24.2)	440 (63.8)
≥10	2,435 (65.5)	2,256 (74.6)	179 (25.9)
Unknown	108 (2.9)	37 (1.2)	71 (10.3)
Use of concomitant ASMs at baseline	3,654 (98.3)	3,000 (99.1)	654 (94.8)
Number of concomitant ASMs[cd]			
1	1,191 (32.6)	725 (24.2)	466 (71.3)
2	947 (25.9)	815 (27.2)	132 (20.2)
≥3	1,516 (41.5)	1,460 (48.7)	56 (8.6)
Psychiatric comorbidity within 2 years prior to study	597 (16.1)	513 (17.0)	84 (12.2)
Aggression[bc]	224 (37.5)	191 (37.2)	33 (39.3)
Depression[bc]	203 (34.0)	162 (31.6)	41 (48.8)
Suicide-related behaviour[bc]	11 (1.8)	10 (1.9)	1 (1.2)
Other[bc]	260 (43.6)	233 (45.4)	27 (32.1)

Data are presented as n (%) unless otherwise stated. ASM: anti-seizure medication; BMI: body mass index; FBTCS: focal to bilateral tonic-clonic seizure; FS: focal seizure; GTCS: generalised tonic-clonic seizure; PER: perampanel; SD: standard deviation.

[a] Within the 28 days prior to starting PER therapy. [b] Duplicates were allowed. [c] Tabulation of participants for which the response was "yes". [d] Drugs were tabulated according to generic name.

± 1.5 mg/d, and the maximum doses were 4.7 ± 2.7 mg/d, 5.0 ± 2.8 mg/d and 3.5 ± 2.1 mg/d, respectively. *Figure 1* shows the PER retention rate, calculated using the Kaplan-Meier method. The retention rates at 52 weeks for all patients included in the safety analysis dataset, patients younger than 65 years, and patients 65 years of age or older were 58.5%, 59.7%, and 53.3%, respectively.

The major factors leading to withdrawal at 24 weeks were AEs in 62.0%, 65.2%, and 51.6%, not visiting the hospital midway through the assessment period in 18.8%, 14.4%, and 32.6%, and inadequate drug response in 18.5%, 21.7%, and 8.4% of all patients, patients younger than 65 years, and patients aged 65 years or older, respectively. The major reasons leading to withdrawal at 52 weeks were an inadequate drug response in 40.2%, 44.1%, and 8.8%, AEs in 36.6%, 37.9%, and 26.5%, and not visiting the hospital midway through the assessment period in 27.8%, 23.2%, and 64.7% of the groups, respectively. The proportion of patients who did not visit the hospital midway through the assessment period was higher in patients 65 years of age or older compared with that in patients younger than 65 years.

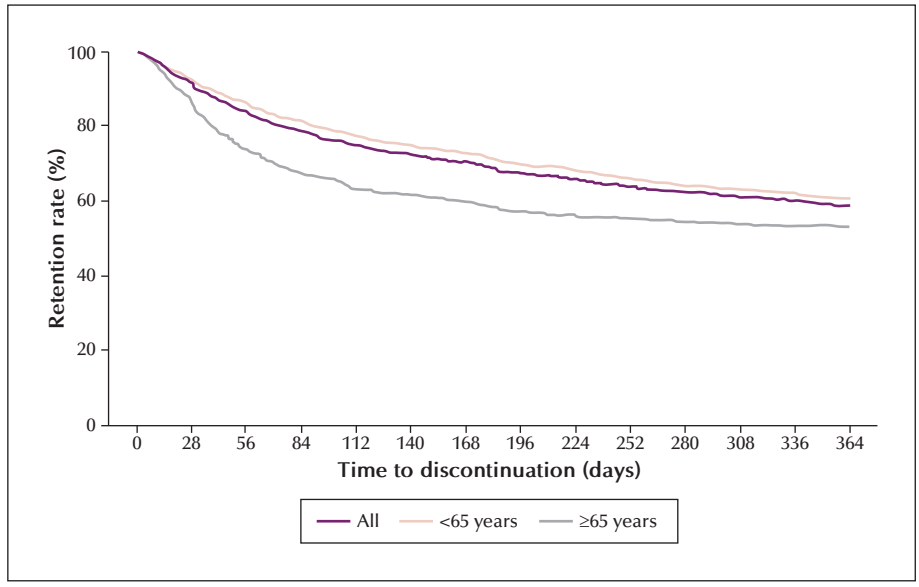
Safety outcomes

AEs were reported for 1,465 (39.4%) patients, and serious AEs (SAEs) occurred in 181 (4.9%) patients based on the safety analysis dataset. ADRs were reported for 1,247 (33.6%) patients. The incidences in patients younger than 65 years and those 65 years of age or older were 36.2% and 22.2%, respectively. The most common ADRs were somnolence (11.6% and 5.5%), dizziness (9.7% and 5.4%) and irritability (4.7% and 1.2%) (*table 2*). Serious ADRs (SADRs) occurred in 63 patients (1.7%). SADRs that occurred in five or more patients were aggression, agitation, and dizziness, and there was no marked difference in the frequency or type of these SADRs between the two age groups (*table 2*).

Falls due to AEs, such as dizziness, occurred in 21 (0.6%) of the patients in the safety analysis dataset. Of those aged 65 years or older, falls occurred in seven (1.0%) patients. Fourteen (0.5%) patients younger than 65 years of age experienced falls. We performed a multivariate analysis to investigate the characteristic factors affecting the occurrence of ADRs in the patient sample (*supplementary table 2*). The results showed a significantly higher rate of ADRs according to sex (female), seizure type at baseline (FS with or without FBTCS), aetiology (brain infection), disease duration (≥10 years), psychiatric comorbidity or suicide-related behaviour within two years prior to the start of the study, history of drug allergies, and the number of concomitant oral antiseizure medications (two or more drugs). We observed a significant decrease in ADRs according to age (65 years of age or older) and the co-administration of antiseizure medications that promote PER metabolism.

Efficacy outcomes

The 50% responder rates in patients younger than 65 years and those aged 65 years or older, respectively, were 60.1% (190/316 patients) and 89.0% (73/82) for patients with FAS with motor signs, 48.0% (118/246) and 60.0% (12/20) for FAS without motor signs, 47.4% (614/



■ **Figure 1.** PER retention rate via Kaplan-Meier analysis in all patients and by age subgroup. PER: perampanel.

▼ **Table 2.** Incidence of ADRs.

	All *n* = 3,716		Age <65 years *n* = 3,026		Age ≥65 years *n* = 690	
	All grades	Severe	All grades	Severe	All grades	Severe
Number of patients who experienced ADRs	1,247 (33.6)	63 (1.7)	1,094 (36.2)	48 (1.6)	153 (22.2)	15 (2.2)
Psychiatric disorders						
Irritability	150 (4.0)	1 (0.0)	142 (4.7)	1 (0.0)	8 (1.2)	0 (0.0)
Aggression	64 (1.7)	9 (0.2)	56 (1.9)	7 (0.2)	8 (1.2)	2 (0.3)
Agitation	56 (1.5)	5 (0.1)	51 (1.7)	5 (0.2)	5 (0.7)	0 (0.0)
Anger	51 (1.4)	3 (0.1)	34 (1.1)	2 (0.1)	17 (2.5)	1 (0.1)
Nervous system disorders						
Somnolence	390 (10.5)	2 (0.1)	352 (11.6)	1 (0.0)	38 (5.5)	1 (0.1)
Dizziness	331 (8.9)	5 (0.1)	294 (9.7)	4 (0.1)	37 (5.4)	1 (0.1)
Seizure/epilepsy	56 (1.5)	2 (0.1)	53 (1.8)	2 (0.1)	3 (0.4)	0 (0.0)

Data are presented as n (%).
Only ADRs with an incidence of 1.00% or more were included in this table.
ADR: adverse drug reaction.

1,295) and 80.2% (178/222) for FIAS, 70.8% (426/602) and 93.4% (99/106) for FBTCS, and 63.6% (234/368) and 88.9% (24/27) for GTCS (*figure 2*). The 100% responder rates in patients younger than 65 years and those aged 65 years or older, respectively, were 38.0% (120/316) and 78.0% (64/82) for FAS with motor signs, 27.6% (68/246) and 45.0% (9/20) for FAS without motor signs, 27.0% (350/1,295) and 65.8% (146/222) for FIAS, 56.0% (337/602) and 87.7% (93/106) for FBTCS, and 48.1% (177/368) and 81.5% (22/27) for GTCS.

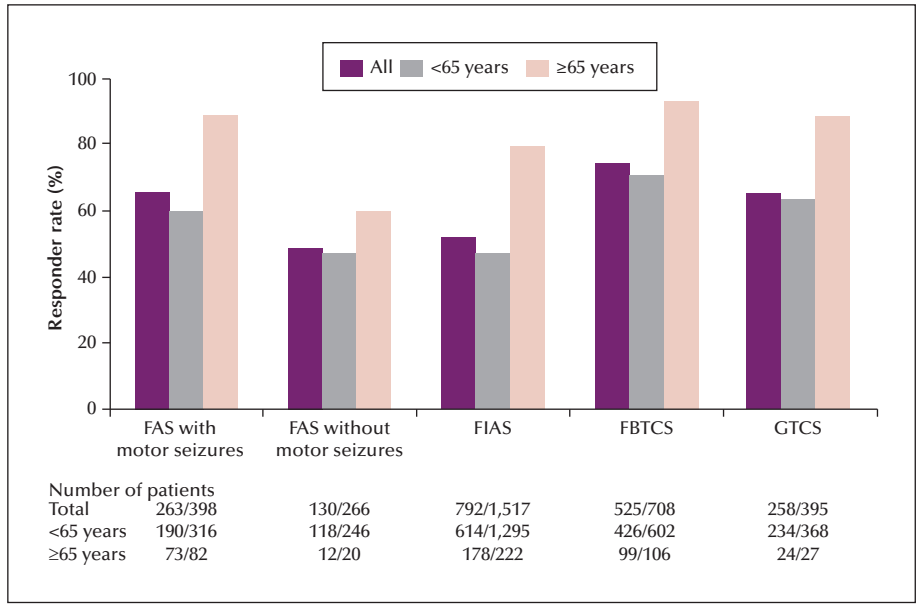
In patients aged <65 years, the median percent change (min, max) in seizure frequency at the LOCF was −66.7 (−100.0, 700.0) for FAS with motor signs, −40.2 (−100.0, 733.3) for FAS without motor signs, −33.3 (−100.0, 1900.0) for FIAS, −100.0 (−100.0, 350.0) for FBTCS, and −81.6 (−100.0, 1300.0) for GTCS. In patients aged ≥65 years, the median percent change in seizure frequency at the LOCF was −100.0 (−100.0, 400.0) for FAS with motor signs, −71.4 (−100.0, 300.0) for FAS without motor signs, −100.0 (−100.0, 300.0) for FIAS, −100.0 (−100.0, 100.0) for FBTCS, and −100.0 (−100.0, 0.0) for GTCS.

We performed a multivariate analysis to investigate the characteristic factors affecting the 50% responder rates in patient subgroups (*supplementary table 3*). The results showed a significant increase in the 50% responder rate with increased age (65 years of age or older), seizure type at baseline (GTCS), epilepsy classification (genetic), and aetiology (brain tumour, cerebrovascular disorder). In contrast, we found a significant decrease in 50% responder rates according to disease duration (≥10 years), history of drug allergies, developmental disability and cognitive impairment, co-administration of anti-seizure medications that promote PER metabolism, and the number of concomitant oral anti-seizure medications (two or more drugs).

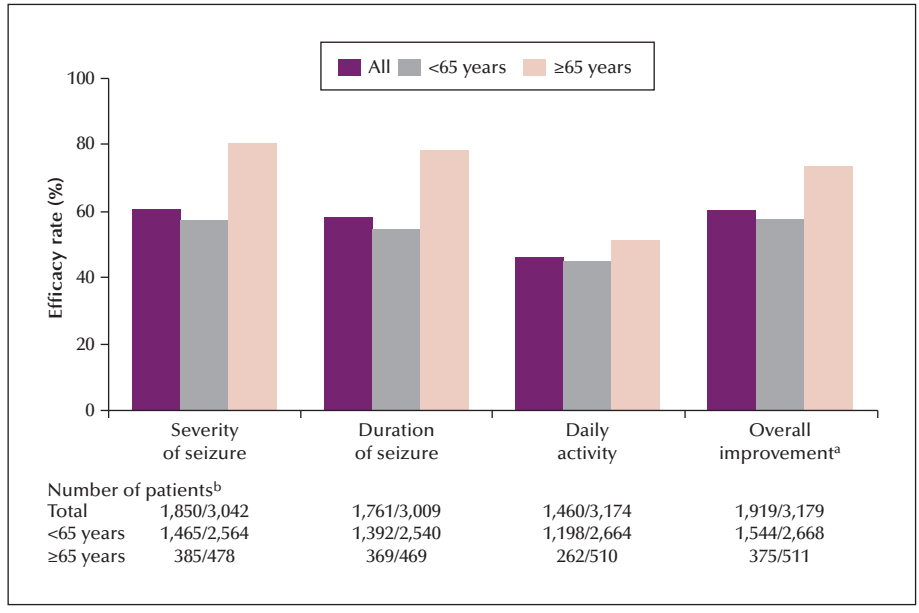
Figure 3 shows the efficacy rates in terms of improvement in symptoms/conditions in the efficacy analysis dataset. The improvement rates in patients younger than 65 years and those aged 65 years or older were 57.1% and 80.5% for seizure severity, 54.8% and 78.7% for seizure duration, 45.0% and 51.4% for daily activities, and 57.9% and 73.4% for overall conditions, respectively.

Discussion

To date, this is the largest real-world observational study to investigate the effects of PER as a treatment for epileptic seizures. Many of the patients in this study had structural etiology, a disease duration of more than 10 years, and a history of multiple concomitant anti-seizure medication use prior to PER administration, suggesting that their seizures were drug resistant. The proportions of patients 65 years of age or older with cerebrovascular disorder, brain tumour, and trauma were higher than those among patients younger than 65 years. This tendency was also observed in a European study [18]. In addition, consistent with the present results, a previous investigation of older epilepsy patients in Japan found that cerebrovascular disorder was the most common aetiology aside from non-lesional epilepsy [19]. In the present study, the proportion of older patients (65 years of age or older) with a



■ **Figure 2.** Responder rates (50%) in all patients and by age subgroup. FBTCS: focal to bilateral tonic-clonic seizure; FIAS: focal impaired awareness seizures; FAS: focal aware seizure; GTCS: generalised tonic-clonic seizure.



■ **Figure 3.** Efficacy rate in terms of overall symptom improvement in the efficacy analysis dataset. [a]Overall judgment of seizure frequency, seizure severity, adverse events, and overall daily living conditions. [b]Total number of cases excluding "undecidable" cases.

disease duration of more than 10 years was relatively low (25.9%). Thus, our analysis dataset may have included a particularly high proportion of older patients who developed symptoms shortly prior to study enrolment.

Safety

Our analysis indicated that the combination of PER with other anti-seizure medications in patients with epilepsy was well tolerated and that long-term treatment was possible in many cases.
The results of our multivariate analysis showed that the incidence of ADRs was significantly increased in patients taking two or more concomitant medications. This supports the notion that, as is the case with other anti-seizure medications, PER treatment in combination with fewer additional drugs (ideally only one) carries a reduced risk of ADRs. Further, the multivariate analysis indicated that the incidence of ADRs was significantly lower in patients aged 65 years or older compared with those aged less than 65 years. This may be attributable to the lower average daily and maximum doses of PER in adults aged 65 years or older, as well as the high proportion of patients taking a single concomitant anti-seizure medication in our sample.

Efficacy

Similar to previous clinical studies, we found that PER in combination with other anti-seizure medication(s) was efficacious in suppressing various types of seizures, including FS with or without FBTCS or GTCS. The 50% responder rates in the patients with these seizure types were comparable to those in previous PER clinical trials [12-14, 20, 21].
Our multivariate analysis of patient characteristics revealed that PER in combination with a single drug significantly reduced seizure frequency. Glauer *et al.* reported that drug combination therapy with 4 mg/d of PER was sufficiently effective such that the number of concomitant drugs could be decreased as the seizures disappeared, thus reducing the patient burden of treatment [22].
Our multivariate analysis indicated that the 50% responder rate was significantly higher in patients aged 65 years age or older compared with those younger than 65 years. This may be attributable to the high proportion of older patients with a disease duration of less than 10 years. Indeed, a previous study found that low doses of anti-seizure medications were effective in older patients with epilepsy, especially those who developed epilepsy at a later age [19]. In a subgroup analysis of 28 elderly patients in a PER Phase 3 study, comparable efficacy was demonstrated between patients aged ≥65 years and those aged <65 years [17].
In a previous long-term analysis, the retention rate of PER at one year was 73.5% [23]. Similarly, a real-world observational study reported that the retention rate of PER at one year was 60.6% [24]. In this study, the retention rate at 12 months was 58.5%, which is comparable to previous studies. This result demonstrates the high tolerability of PER in a real-world setting in Japan.

Limitations

Our study has several limitations that affect the interpretation of our results. First, this study was conducted as part of daily clinical practice, and the participants were not required to complete a seizure diary. Thus, our study may have been less rigorous than a clinical trial that required a seizure diary. Second, in this study, we only evaluated the effects of PER in combination with other anti-seizure medications. Moreover, changes to other anti-seizure medications were allowed. Despite this, we observed no changes in the number of concomitant anti-seizure medications in most patients at the last observation compared with baseline, indicating that concomitant medications had a limited effect. Further studies of PER monotherapy in elderly populations are required. Third, we did not compare our PER data to that from other drugs in terms of differences in safety and efficacy between patients younger than 65 years and those aged 65 years or older. Therefore, we do not know whether our findings are specific to PER treatment.

Conclusion

In this large-scale real-world observational study, we investigated the safety and efficacy of combination therapy with PER in patients with drug-resistant refractory seizures, including those aged 65 years or older. Our data confirmed that relatively low doses of PER had adequate efficacy in reducing seizure frequency. Further, we did not observe any unexpected safety issues, and the major AEs that occurred in the older patient group are already well established. These findings highlight the importance of PER as a clinical treatment option for older patients with seizure disorders. ■

Supplementary material.
Supplementary data accompanying the manuscript are available at www.epilepticdisorders.com.

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Data sharing statement.
Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, therefore supporting data is not available.

References

1. Sillanpää M, Gissler M, Schmidt D. Efforts in epilepsy prevention in the last 40 years: lessons from a large nationwide study. *JAMA Neurol* 2016; 73: 390-5.

2. Ramsay RE, Macias FM, Rowan AJ. Diagnosing epilepsy in the elderly. *Int Rev Neurobiol* 2007; 81: 129-51.

3. Lhatoo SD, Johnson AL, Goodridge DM, MacDonald BK, Sander JW, Shorvon SD. Mortality in epilepsy in the first 11 to 14 years after diagnosis: multivariate analysis of a long-term, prospective, population-based cohort. *Ann Neurol* 2001; 49: 336-44.

4. Liu S, Yu W, Lü Y. The causes of new-onset epilepsy and seizures in the elderly. *Neuropsychiatr Dis Treat* 2016; 12: 1425-34.

5. Hernández-Ronquillo L, Adams S, Ballendine S, Téllez-Zenteno JF. Epilepsy in an elderly population: classification, etiology and drug resistance. *Epilepsy Res* 2018; 140: 90-4.

6. Werhahn KJ, Trinka E, Dobesberger J, Unterberger I, Baum P, Deckert-Schmitz M, *et al*. A randomized, double-blind comparison of antiepileptic drug treatment in the elderly with new-onset focal epilepsy. *Epilepsia* 2015; 56: 450-9.

7. Zilles K, Qü MS, Köhling R, Speckmann EJ. Ionotropic glutamate and GABA receptors in human epileptic neocortical tissue: quantitative in vitro receptor autoradiography. *Neuroscience* 1999; 94: 1051-61.

8. Löscher W, Schmidt D. Epilepsy: perampanel-new promise for refractory epilepsy? *Nat Rev Neurol* 2012; 8: 661-2.

9. Rogawski MA. AMPA receptors as a molecular target in epilepsy therapy. *Acta Neurol Scand Suppl* 2013; 197: 9-18.

10. Hanada T, Hashizume Y, Tokuhara N, Takenaka O, Kohmura N, Ogasawara A, *et al*. Perampanel: a novel, orally active, noncompetitive AMPA-receptor antagonist that reduces seizure activity in rodent models of epilepsy. *Epilepsia* 2011; 52: 1331-40.

11. Turski L, Jacobsen P, Honoré T, Stephens DN. Relief of experimental spasticity and anxiolytic/anticonvulsant actions of the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate antagonist 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(F) quinoxaline. *J Pharmacol Exp Ther* 1992; 260: 742-7.

12. 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: 589-96.

13. 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: 117-25.

14. 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: 1408-15.

15. Yamamoto T, Lim SC, Ninomiya H, Kubota Y, Shin WC, Kim DW, *et al*. Efficacy and safety of perampanel monotherapy in patients with focal-onset seizures with newly diagnosed epilepsy or recurrence of epilepsy after a period of remission: the open-label Study 342 (FREEDOM Study). *Epilepsia Open* 2020; 5: 274-84.

16. Steinhoff BJ, Patten A, Williams B, Malhotra M. Efficacy and safety of adjunctive perampanel 4 mg/d for the treatment of focal seizures: a pooled post hoc analysis of four randomized, double-blind, phase III studies. *Epilepsia* 2020; 61: 278-86.

17. Leppik IE, Wechsler RT, Williams B, Yang H, Zhou S, Laurenza A. Efficacy and safety of perampanel in the subgroup of elderly patients included in the phase III epilepsy clinical trials. *Epilepsy Res* 2015; 110: 216-20.

18. Stefan H, May TW, Pfäfflin M, Brandt C, Füratsch N, Schmitz B, *et al*. Epilepsy in the elderly: comparing clinical characteristics with younger patients. *Acta Neurol Scand* 2014; 129: 283-93.

19. Tanaka A, Akamatsu N, Shouzaki T, Toyota T, Yamano M, Nakagawa M, *et al*. Clinical characteristics and treatment responses in new-onset epilepsy in the elderly. *Seizure* 2013; 22: 772-5.

20. French JA, Gil-Nagel A, Malerba S, Kramer L, Kumar D, Bagiella E. Time to prerandomization monthly seizure count in perampanel trials: a novel epilepsy endpoint. *Neurology* 2015; 84: 2014-20.

21. Nishida T, Lee SK, Inoue Y, Saeki K, Ishikawa K, Kaneko S. Adjunctive perampanel in partial-onset seizures: Asia-Pacific, randomized phase III study. *Acta Neurol Scand* 2018; 137: 392-9.

22. Glauser T, Laurenza A, Yang H, Williams B, Ma T, Fain R. Efficacy and tolerability of adjunct perampanel based on number of antiepileptic drugs at baseline and baseline predictors of efficacy: a phase III post-hoc analysis. *Epilepsy Res* 2016; 119: 34-40.

23. Krauss GL, Perucca E, Kwan P, Ben-Menachem E, Wang XF, Shih JJ, *et al*. Final safety, tolerability, and seizure outcomes in patients with focal epilepsy treated with adjunctive perampanel for up to 4 years in an open-label extension of phase III randomized trials: study 307. *Epilepsia* 2018; 59: 866-76.

24. 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.

TEST YOURSELF

(1) What is the current gap in the literature regarding the use of perampanel in patients with drug-resistant refractory seizures?

(2) What factors were found to be significantly associated with the incidence of adverse drug reactions among patients treated with perampanel in the current study?

(3) What factors were found to be significantly associated with a decrease in the 50% responder rate?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.