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Long-term safety and seizure outcome in Japanese patients with Lennox–Gastaut syndrome receiving adjunctive rufinamide therapy: An open-label study following a randomized clinical trial

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ABSTRACT

Purpose: To evaluate the long-term safety and seizure outcome in Japanese patients with Lennox–Gastaut syndrome (LGS) receiving adjunctive rufinamide therapy.
Subjects and methods: We conducted an open-label extension study following a 12-week multicenter, randomized, double-blind, placebo-controlled study of adjunctive rufinamide therapy in Japanese patients with LGS. Fifty-four patients participated in the extension study. Seizure frequency was evaluated until 52 weeks after the start of the extension study. Adverse events (AEs) were evaluated throughout both studies.
Key findings: Of the 54 patients, 41 (75.9%) completed the extension study. The median duration of exposure to rufinamide was 818.0 days in all 54 patients, and 38 patients (70.4%) received rufinamide for 2 years or more. The median percent change in the frequency of tonic–atonic seizures relative to the frequency at the start of the double-blind study was −39.3% (12 weeks), −40.6% (24 weeks), −46.8% (32 weeks), −47.6% (40 weeks), and −36.1% (52 weeks). Reduction of total seizure frequency was also maintained until 52 weeks. Frequent treatment-related AEs were somnolence (20.4%), decreased appetite (16.7%), transient seizure aggravation including status epilepticus (13.0%), vomiting (11.1%), and constipation (11.1%). Adverse events were mild or moderate, except for transient seizure aggravation in three patients. Adverse events resulting in discontinuation of rufinamide were decreased appetite, drug eruption, and worsening of underlying autism. When clinically notable weight loss was defined as a decrease ≥7% relative to baseline, 22 patients (40.7%) experienced weight loss at least once during long-term observation, although weight loss was reported as an AE in only three patients.
Significance: This study demonstrated a long-term benefit of rufinamide as adjunctive therapy for Japanese patients with LGS. Exacerbation of seizures and decreased appetite/weight loss should be monitored carefully.

1. Introduction

Lennox–Gastaut syndrome (LGS) is an epileptic encephalopathy characterized by various types of epileptic seizures (mainly tonic seizures), diffuse slow spike-and-wave complex patterns on the electroencephalogram (EEG), and impairment of cognitive function. The long-term prognosis for mental function and seizures is generally devastating (Arzimanoglou et al., 2009; Beaumanoir, 1985; Blatter-Arifi, 1991; Oguni et al., 1996; Ohtsuka et al., 1990;

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Yagi, 1996). A high risk of sudden falls due to tonic and/or atonic seizures often affects the quality of life.

Rufinamide is a triazole derivative with a different structure to other antiepileptic drugs (AEDs). It has been found that rufinamide modulates the frequency of sodium-dependent neuronal action potentials in cultured spinal cord neurons (McLean et al., 2005). In addition, recent basic research using recombinant technology demonstrated that the primary target of rufinamide in the human brain seems to be a particular isoform of the voltage-gated sodium channel ($N_{av}1.1$) (Gilchrist et al., 2014). The effectiveness of rufinamide as adjunctive therapy for LGS was established by a double-blind, randomized, placebo-controlled study (Glauser et al., 2008) and also by our recent study in Japanese patients (Ohtsuka et al., 2014).

Our recent study demonstrated that adjunctive therapy with rufinamide significantly reduced the frequency of tonic–atonic seizures by 24.2% compared with 3.3% in the placebo group ($p = 0.003$), and also reduced total seizure frequency by 32.9% compared with 3.1% in the placebo group ($p < 0.001$). The rufinamide group showed a significantly higher responder rate of tonic–atonic seizures than the placebo group and rufinamide treatment was generally well tolerated, with decreased appetite, somnolence, and vomiting being the most frequent treatment-related adverse events (AEs). Here we report the results of an open-label extension study that was performed after the above-mentioned double-blind study.

2. Subjects and methods

2.1. Study design

This was an open-label extension study following a 12-week multicenter, randomized, double-blind, placebo-controlled study of adjunctive rufinamide therapy in Japanese patients with LGS (Ohtsuka et al., 2014). In the preceding placebo-controlled study, eligible patients were aged 4–30 years and weighed 15 kg or more at baseline. Lennox–Gastaut syndrome was diagnosed from a history of tonic and/or atonic seizures and atypical absence seizures with slow spike-and-wave complex patterns on the EEG within 6 months before the baseline period. Eligible patients had experienced at least 90 seizures during the 28 days before the baseline period, and were taking between one and three AEDs. Patients were excluded from the study if tonic–clonic status epilepticus occurred during the baseline period. Patients were also excluded if they had other severe medical conditions or electrocardiographic/laboratory abnormalities.

This extension study consisted of three periods: a pre-conversion period (maximum of four weeks for fixation of data from the preceding double-blind study), a conversion period, and a maintenance period. During the conversion period, placebo was gradually replaced by rufinamide within two weeks under double-blind conditions. The maintenance period of the study continued until rufinamide was released in Japan (May 2013). Fifty-four patients participated in the extension study. Hospital visits were scheduled at 4, 8, 12, 18, 24, 32, and 40 weeks, then every 12 weeks as the extension study continued. The primary objective of the extension study was to evaluate the long-term safety of adjunctive therapy with rufinamide, and the secondary objective was to evaluate seizure outcomes with this therapy. Therefore, we assessed safety variables at all hospital visits throughout the extension study in all 54 patients, as well as during the double-blind placebo-controlled study. On the other hand, the efficacy variable (seizure frequency) was only assessed at 12, 24, 32, 40, and 52 weeks. Patients who discontinued the extension study before the 12-week point were excluded from the analysis of seizure outcomes.

Rufinamide was administered twice a day and the daily dose was determined individually based on body weight. Dose reduction by one level (approximately 25% according to dose titration schedule in the preceding placebo-controlled study) was allowed if the investigator judged that it was necessary for safety (Ohtsuka et al., 2014). The number and types of concomitant AEDs could be changed during the extension study, but administration of more than three concomitant AEDs with rufinamide was not allowed. Rescue treatment (e.g. intravenous or rectal diazepam) was also permitted for transient seizure aggravation including status epilepticus.

Seizure frequency was determined from a diary recorded by the caregivers (mainly parents, but also including schoolteachers and childcare workers). During the extension study, caregivers were instructed to record data in the seizure diary for the 7-day period after each designated hospital visit (12, 24, 32, 40, and 52 weeks). This was done to reduce the burden on caregivers while still evaluating the change in seizure frequency consistently throughout the extension study. Seizures were classified according to the International League Against Epilepsy (ILAE) Classification of Epileptic Seizures (Commission on Classification and Terminology of the ILAE, 1981). Amelioration of tonic seizures and/or atonic seizures is essential for LGS patients, since these seizures often result in sudden falls and disturb the patients' quality of life. Referring to the previous study (Glauser et al., 2008), the sum of frequencies of tonic seizures and atonic seizures was defined as the frequency of tonic–atonic seizures. The percent change of seizure frequency was calculated as $[(M - B)/B] \times 100$, where M was the seizure frequency during the maintenance period of the extension study and B was the seizure frequency during the baseline period of the preceding placebo-controlled study. The 50% responder rate was calculated as the percentage of patients with at least 50% reduction in the frequency of seizures.

In all 54 patients who participated in the extension study, AEs were evaluated throughout the entire rufinamide treatment period, including the preceding placebo-controlled study. Adverse events were assessed by an investigator at each visit and the investigator also classified the severity of each AE as mild (tolerable and not interfering with daily activities), moderate (interfering with daily activities) or severe (severely disabling). The relationship of each AE with rufinamide was categorized by the investigator as "not related", "possibly related", or "probably related". Treatment-related AEs were defined as "possibly related" or "probably related" AEs. In addition, clinical laboratory tests, body weight, and the electrocardiogram (ECG) were evaluated.

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice for trials of medical products and was approved by the ethical committee of each participating hospital. Written informed consent was obtained from the legal guardians and/or the patients prior to participation in the extension study.

2.2. Statistical methods

Because this was an open-label extension study, descriptive statistics were calculated for continuous variables and categorical variables. The percentage, median, mean, and standard deviation were calculated for the demographic profile, seizure outcomes, and safety variables. Patients with no seizure data were excluded from the analysis of seizure outcome.

In children aged ≤15 years, the absolute body weight was measured and it was also calculated as a ratio relative to the average weight for Japanese children according to Japanese government statistics (Kato et al., 2014; Ministry of Education, Culture, Sports, Science and Technology, 2012) to allow for the influence of developmental weight gain.

Electrocardiographic data were obtained digitally and ECG parameters were calculated automatically. The QT interval was corrected for heart rate (QTc) according to Bazett's formula: QT interval*(60/heart rate)$^{1/2}$.

The last observation carried forward method was employed to handle missing data.

3. Results

3.1. Patient profile

All 54 patients who completed the preceding placebo-controlled study participated in this extension study (Fig. 1). Forty-one (75.9%) patients completed the extension study and 13 patients (24.1%) discontinued rufinamide treatment. The reasons for discontinuation of rufinamide were lack of efficacy (13.0%), AEs (7.4%), and other reasons (3.7%). Seizure outcomes were evaluated in 46 of the 54 patients. The median duration of exposure to rufinamide was 818.0 days (range: 13.5–1042.5 days) in all 54 patients, while it was 859.5 days (range: 164.0–1042.5 days) in the 46 patients evaluated for seizures. Thirty-eight patients (70.4%) received treatment with rufinamide for at least 2 years.

The mean daily dosage [mean ± standard deviation (SD)] was 40.7 ± 6.8 mg/kg, while the daily dosage stratified by body weight was as follows: 989.9 ± 43.1 mg (15.0–30.0 kg), 1607.3 ± 261.8 mg (30.1–50.0 kg), 2306.8 ± 198.6 mg (50.1–70.0 kg), and 3042.6 ± 266.1 mg (≥70.1 kg).

In the safety analysis set, consisting of all 54 patients in the extension study, the mean baseline age of the patients [mean ± SD] was 15.0 ± 6.8 years (Table 1). Twenty-two patients (40.7%) were aged 4–11 years, 11 (20.4%) were aged 12–16 years, and 21 (38.9%) were ≥17 years old. The common underlying causes were tuberous sclerosis and cerebral palsy (five patients each), followed by cerebral dysgenesis, encephalitis, and bacterial meningitis (three patients each).

Patients were taking one (3 patients, 5.6%), two (12 patients, 22.2%) or three (39 patients, 72.2%) concomitant AEDs at the start of the extension study and also at baseline. Concomitant AEDs used by >10% of the patients at the start of the extension study were valproic acid (49 patients, 90.7%), lamotrigine (34 patients, 63.0%), clobazam (16 patients, 29.6%), phenytoin (12 patients, 22.2%), carbamazepine (8 patients, 14.8%), and clonazepam (7 patients, 13.0%) as shown in Table 1. Forty-one patients (75.9%) continued the same concomitant AEDs throughout the extension study. In the 46 patients whose seizure outcomes were evaluated, the changes of the concomitant AEDs by 52 weeks after the start of the extension study were as follows: addition of one AED in four patients, switching of AEDs without changing the number of concomitant AEDs in four patients, and deletion of one AED in five patients. Other treatments, such as vagus nerve stimulation or a ketogenic diet, were not performed in any of the patients. Reduction of the dose of rufinamide by one level was done in six patients during the extension study.

Table 1
Demographic and baseline characteristics of the 54 patients in the extension study.

Male, *n* (%)	33 (61.1)
Mean age (SD), years	15.0 (6.8)
Mean weight (SD), kg	39.8 (18.5)
Mean time after diagnosis of LGS (SD), years	10.0 (6.5)
Underlying cause, *n* (%)	25 (46.3)
Seizure type, *n* (%)	
Multiple seizure types	40 (74.1)
Tonic–atonic seizures only	14 (25.9)
Tonic–atonic seizure frequency,[a] median (range)	227.1 (8.3–22,469.5)
Total seizure frequency,[a] median (range)	274.0 (63.0–22,499.4)
No. of concomitant AEDs, *n* (%)	
One	3 (5.6)
Two	12 (22.2)
Three	39 (72.2)
Concomitant AEDs,[b] *n* (%)	
Valproic acid	49 (90.7)
Lamotrigine	34 (63.0)
Clobazam	16 (29.6)
Phenytoin	12 (22.2)
Carbamazepine	8 (14.8)
Clonazepam	7 (13.0)

LGS, Lennox–Gastaut syndrome; AED, antiepileptic drug.
[a] Seizure frequency per 28 days.
[b] Concomitant AEDs used by at least 10% of patients at the start of the extension study.

3.2. Seizure outcome

Eight of the 54 patients were excluded from the analysis of seizure outcomes due to lack of seizure data because of early discontinuation before the 12-week point of the extension study. Seizure outcomes were evaluated in the remaining 46 patients. The median percent change in the frequency of tonic–atonic seizures relative to baseline was −39.3% at 12 weeks, −40.6% at 24 weeks, −46.8% at 32 weeks, −47.6% at 40 weeks, and −36.1% at 52 weeks (Fig. 2). The median percent change of total seizure frequency relative to baseline was −47.7% at 12 weeks, −48.9% at 24 weeks, −50.6% at 32 weeks, −52.0% at 40 weeks, and −47.4% at 52 weeks. At the last observation, 43.5% of the patients showed ≥50% reduction

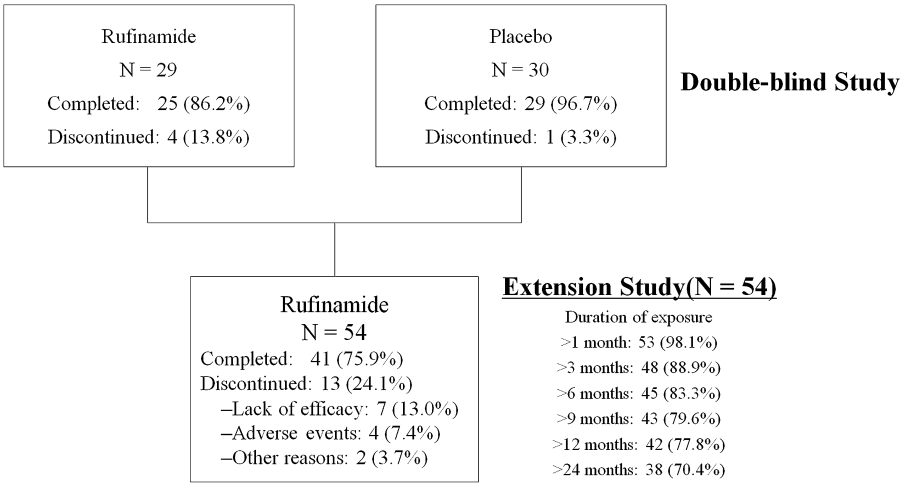

Fig. 1. Disposition of the patients.

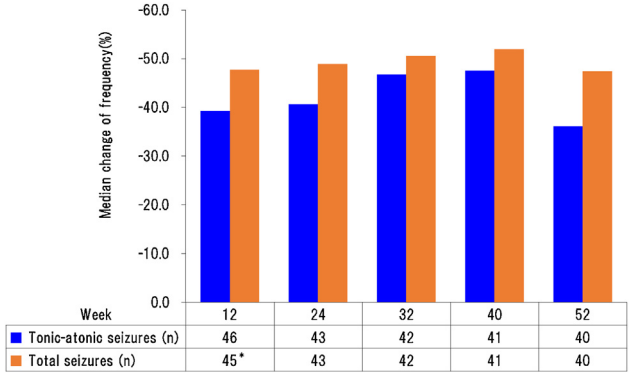

Fig. 2. Median percent changes of the tonic–atonic seizure frequency and total seizure frequency relative to baseline during the extension study. *One patient was excluded from analysis of total seizure frequency at 12 weeks because the number of myoclonic seizures was not recorded in the seizure diary.

of total seizure frequency, including 39.1% of patients with ≥50% reduction of tonic–atonic seizures and 37.5–85.7% of patients with ≥50% reduction of other types of seizures (Table 2). One patient (2.2%) was completely free from seizures at the last observation, whereas five patients (10.9%) showed a ≥25% increase of total seizure frequency relative to baseline.

3.3. Safety

Adverse events occurred in all 54 patients and treatment-related AEs occurred in 38 patients (70.4%) during the entire study period, including the preceding placebo-controlled study (Table 3). The common treatment-related AEs were somnolence (11 patients, 20.4%), decreased appetite (9 patients, 16.7%), transient seizure aggravation including status epilepticus (7 patients, 13.0%), and vomiting and constipation (6 patients each, 11.1%).

All AEs were mild or moderate, except for transient seizure aggravation in three patients. A 19-year-old woman experienced exacerbation of tonic seizures on Day 717 of rufinamide administration, and was admitted to hospital. Her symptoms gradually resolved after she received intravenous phenytoin and she returned to the previous state by 17 days after the onset. In addition, a 12-year-old boy developed nonconvulsive status epilepticus on Day 207 of rufinamide administration. By adjusting the doses of concomitant AEDs (increasing valproate and decreasing phenobarbital), his nonconvulsive status epilepticus resolved after 17 days. The third patient was a 15-year-old girl who developed nonconvulsive status epilepticus on Day 434 of rufinamide administration. It resolved soon after administration of a diazepam suppository. The first two patients had not experienced the same type of seizure exacerbation before participating in this study. In all three patients, exacerbation was evaluated as a treatment-related AE. In this study, investigators performed comprehensive assessment of the severity and frequency of seizures before deciding whether seizure exacerbation was a treatment-related AE.

Adverse events resulted in discontinuation of rufinamide in four patients, with the events being decreased appetite in two patients (3.7%), drug eruption in one patient (1.9%), and worsening of underlying autism in one patient (1.9%). All of these events resolved without sequelae after discontinuation of rufinamide.

Decreased appetite is one of the characteristic AEs associated with rufinamide. Its incidence was higher in patients aged ≥17 years than in the other age groups [1/22 patients (4.5%) aged 4–11

Table 2
Numbers of patients with 100% reduction, ≥50% reduction, and ≥25% increase of seizure frequency at final observation.

Seizure type	n[a]	100% reduction	≥50% reduction	≥25% increase
Tonic–atonic seizures	46	4(8.7)	18(39.1)	5(10.9)
Tonic seizures	45	4(8.9)	18(40.0)	6(13.3)
Atonic seizures	16	6(37.5)	11(68.8)	2(12.5)
Atypical absence seizures	24	13(54.2)	18(75.0)	2(8.3)
Myoclonic seizures	14	8(57.1)	9(64.3)	2(14.3)
Tonic–clonic seizures	8	2(25.0)	3(37.5)	1(12.5)
Partial seizures	7	3(42.9)	6(85.7)	1(14.3)
Total seizures	46	1(2.2)	20(43.5)	5(10.9)

Number of patients (%).
[a] Number of patients with a given type of seizure during the baseline period.

Table 3
Common adverse events and treatment-related adverse events.

	AEs, n (%)	Treatment-related AEs, n (%)	Severity of AEs, n		
			Mild	Moderate	Severe
All events	54(100.0)	38(70.4)	28	23	3
Nasopharyngitis	29(53.7)	1(1.9)	29	0	0
Transient seizure aggravation	23(42.6)	7(13.0)	11	9	3
Somnolence	18(33.3)	11(20.4)	15	3	0
Vomiting	15(27.8)	6(11.1)	13	2	0
Influenza	12(22.2)	0	10	2	0
Contusion	12(22.2)	0	11	1	0
Decreased appetite	11(20.4)	9(16.7)	7	4	0
Constipation	9(16.7)	6(11.1)	9	0	0
Dental caries	9(16.7)	0	9	0	0
Upper respiratory tract infection	8(14.8)	0	7	1	0
Stomatitis	6(11.1)	2(3.7)	6	0	0
Pyrexia	6(11.1)	0	6	0	0
Bronchitis	6(11.1)	0	6	0	0
Insomnia	6(11.1)	2(3.7)	5	1	0
Epistaxis	6(11.1)	1(1.9)	6	0	0

AE, adverse event.

years, 2/11 (18.2%) patients aged 12–16 years, and 8/21 (38.1%) patients ≥17 years old]. When we defined clinically notable weight loss as a decrease of weight by ≥7% relative to baseline, it occurred in 22 (40.7%) patients at least once during the observation period. However, weight loss was judged to be an AE by the investigators in only 3 patients (a 5-year-old boy, a 16-year-old girl, and a 20-year-old woman). In this study, the investigators did not have a quantitative definition to guide them when deciding whether weight loss was an AE. The mean percent change of body weight from baseline in each age category is presented in Fig. 3. In patients aged ≥17 years, decreased appetite and weight loss tended to be associated with longer exposure to rufinamide. In patients aged ≤15 years, the weight ratio (mean ± SD) relative to the average weight of healthy Japanese children was 0.86 ± 0.22 at baseline, while it was 0.75 ± 0.19 after 1 year, 0.74 ± 0.17 after 2 years, and 0.75 ± 0.13 after 3 years of exposure to rufinamide. There were no differences between boys and girls.

Electrocardiographic findings reported as treatment-related AEs were ventricular arrhythmia, sinus arrhythmia, and QT prolongation in one patient (1.9%) each. All of these changes were mild and were not seen on subsequent ECGs without discontinuation of rufinamide. There were no differences of ECG parameters between baseline and final observation. In particular, QTc (mean ± SD) was 412.2 ± 27.5 ms at baseline and 407.4 ± 24.6 ms at final observation, with the mean change of QTc from baseline being −4.8 ± 32.2 ms.

All of the abnormal clinical laboratory test results reported as treatment-related AEs only occurred in one patient each.

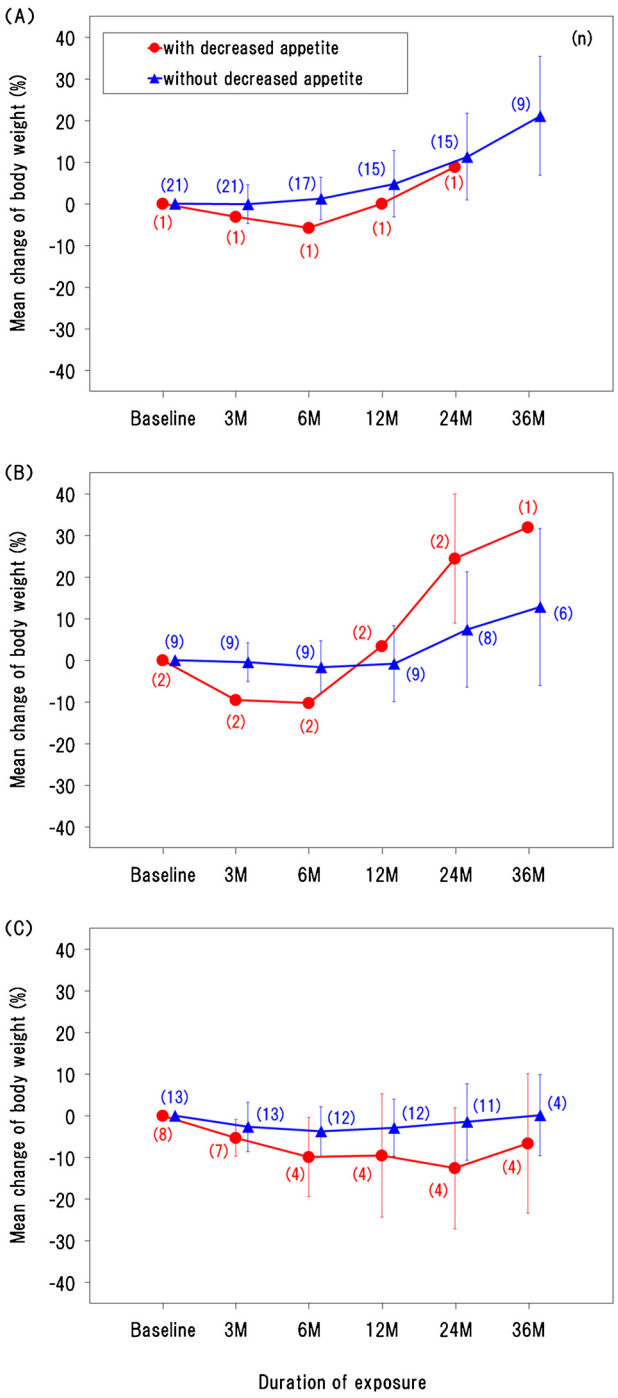

Fig. 3. Mean percent changes of body weight in patients with (red) or without (blue) decreased appetite during the extension study. (A) Patients aged 4–11 years; (B) patients aged 12–16 years; (C) patients aged 17 years or older; (%), number of patients; M, month. Error bars represent SD.

4. Discussion

This extension study demonstrated that rufinamide maintained seizure control over the long term and that there was a relatively high retention rate of rufinamide therapy beyond 2 years. In the present study, we adopted intermittent assessment (seven days after each outpatient visit) to evaluate the changes of seizure frequency while reducing the burden on caregivers. This method of assessment might potentially be less accurate compared with the preceding double-blind study during which seizure diaries were recorded for the entire study period. However, we were able to confirm that efficacy of rufinamide was maintained throughout the extension study without large fluctuations and the long-term seizure outcome in the present study was compatible with the results of other long-term studies on rufinamide (Kluger et al., 2010a,b; Coppola et al., 2010; Kim et al., 2012; Thome-Souza et al., 2014; Kessler et al., 2015). In addition, the high retention rate in the present study indicates that this drug has a favorable risk/benefit balance for Japanese patients with LGS. It was recently suggested that the mechanism of drug resistance in some types of epilepsy (including LGS) involves over-expression of P-glycoprotein in the endothelium of the blood–brain barrier (Zhang et al., 2012; Kumar et al., 2014). It is thought that penetration of the blood–brain barrier by rufinamide is not affected because it is not a substrate of human P-glycoprotein (Chan et al., 2014), and this pharmacological characteristic may be related to its long-term effectiveness for LGS.

During the present long-term study, the safety profile of rufinamide was similar to that revealed by the preceding placebo-controlled study (Ohtsuka et al., 2014) and we did not find any new late-onset AEs. A recent review of rufinamide also suggested that this drug has a favorable risk/benefit profile with a low risk of exacerbating seizures (Coppola et al., 2009). While it is known that some AEDs may cause worsening of seizures, the precise mechanisms underlying this paradoxical effect have not been clarified (Gayatri and Livingston, 2006). According to the National Institute for Health and Care Excellence (NICE) guideline, carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine, and vigabatrin are not recommended for patients with LGS due to the possibility of exacerbating seizures (Nunes et al., 2012). Transient seizure aggravation was one of the common treatment-related AEs in our study and there were some severe events, suggesting that patients should be closely monitored for changes in the frequency and severity of seizures during administration of rufinamide, although transient exacerbation may also represent natural fluctuation of seizure frequency in LGS.

Regarding weight loss, it is notable that 40.7% of patients showed weight loss (≥7% decrease relative to baseline) in our study, although it was not severe in most cases. We also saw a tendency for children taking rufinamide to not show appropriate developmental weight gain with increasing age. Therefore, it seems to be important to carefully monitor body weight during long-term rufinamide therapy and adjust the dosage if necessary. It is known that topiramate, zonisamide, and felbamate, which are often used for the treatment of LGS, can induce weight loss (Ben-Menachem, 2007). Accordingly, combined use of these AEDs with rufinamide would require caution.

In healthy volunteers, rufinamide induced a dose-related decrease of QTc by approximately 20 ms. QT shortening may increase the risk of sudden death and ventricular arrhythmias, and clinically relevant shortening of QTc has been defined as reduction of 80 ms from baseline and/or a QTc duration of 320 ms or less (Shah, 2010). In the present study, QTc only showed a slight decrease (-4.8 ± 32.2 ms), which seems unlikely to be clinically relevant, and few ECG findings were reported as treatment-related AEs. These results indicate that there is no significant cardiovascular risk associated with long-term administration of rufinamide.

There is still a lack of sufficient evidence about the efficacy and safety of rufinamide. While the present study provided useful supporting evidence regarding the favorable profile of rufinamide, the results must be interpreted with caution due to its open-label design and lack of a control group. The other main limitation of this study was that the number of patients was too small to analyze the characteristics of subgroups such as responders, patients with transient seizure aggravation, and patients with weight loss and/or decreased appetite. Lastly, the intermittent assessment procedure adopted in this extension study might not have provided sufficient data to evaluate seizure control. Accordingly, larger-scale clinical trials will be needed to clarify the specific clinical factors related to maintenance of seizure control and the safety of rufinamide.

5. Conclusion

We performed an open-label extension study to evaluate the long-term safety and seizure outcome in Japanese patients with LGS receiving adjunctive rufinamide therapy. Reduction of total seizure frequency, including tonic–atonic seizures, was maintained up to 52 weeks and 75.9% of patients completed the extension study. Most AEs associated with rufinamide therapy were mild or moderate, although exacerbation of seizures and decreased appetite/weight loss require attention.

Disclosure

Yoko Ohtsuka serves as a consultant for Eisai Co., Ltd. and Hiroki Takano is an employee of Eisai Co., Ltd. The remaining authors were study investigators. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Eisai Co., Ltd. (Tokyo, Japan) was solely responsible for the design and conduct of the study as well as the collection, management, and analysis of the data. This study was also supported by grant from Japanese government which was specifically aimed to resolve 'Drug Lag' problem in Japan.

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