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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.