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The Efficacy and Tolerability of Rufinamide in Intractable Pediatric Epilepsy

Jae Yeon Kim, MD[1], Cha Gon Lee, MD[2], Hee Joon Yu, MD[1], Sook Hyun Nam, MD[1], Jeehun Lee, MD[1], Munhyang Lee, MD, PhD[1]

[1]Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, [2]Department of Pediatrics, Eulji Medical Center, Eulji University School of Medicine, Seoul, Korea

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Corresponding author: Munhyang Lee
Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 135-710, Korea
Tel. +82-2-3410-3539, 3522
Fax. +82-2-3410-0043
E-mail; mhlee091@skku.edu

Background and Purpose: Rufinamide (RUF) is a novel antiepileptic drug (AED) and its efficacy has been proven in Lennox-Gastaut syndrome (LGS). However, there is a lack of data regarding the efficacy in pediatric intractable epilepsies other than LGS. The purpose of the study was to explore the efficacy and tolerability of RUF in pediatric patients with intractable epilepsies as well as LGS.

Methods: This retrospective observation study was conducted in Samsung medical center from August 2010 to September 2011. Thirty seven patients (27 males, 10 females, aged between 1.8 and 18.4 years), with refractory epilepsies or LGS were treated with RUF as an adjunctive drug. Efficacy was represented by the response rate and retention rate over the study period. Tolerability was measured as the number of patients who showed adverse effects.

Results: The overall response rate was 21.6% during the 12 months of the study period with 5.4% of seizure-free patients. The retention rate was 54% and ineffectiveness was the most common reason for discontinuation of RUF. The most common adverse effects were insomnia and somnolence.

Conclusions: RUF may be considered to be an efficacious and safe AED for pediatric patients with intractable epilepsies as well as LGS. **(2012;2:33-37)**

Key words: Rufinamide; Efficacy; Children

Introduction

Rufinamide (RUF) is a triazole derivative that is structurally unrelated to other antiepileptic drugs (AED).[1] It was approved by the United States, Food and Drug Administration (FDA) in 2004 for the treatment of Lennox-Gastaut syndrome (LGS) in patients aged 4 years and older.[2] RUF was authorized for the same indication in Europe in January 2007.[2,3] The mechanism of action involves limiting the firing of excessive sodium-dependent action potentials.[1] RUF has been reported to reduce the number of drop attacks and major motor seizure in about 60% of patients with LGS and has subsequently been regarded as an effective adjunctive therapeutic agent.[2] In recent years, studies have been reported that RUF is also efficacious and well tolerated in the treatment of various epilepsy syndromes other than LGS, including cases of refractory epilepsy in pediatric patients.[3] However, there are still limited data regarding the long term treatment results of RUF for pediatric refractory epilepsy. The aim of this study was to delineate the long term efficacy and tolerability of RUF in children and infants with intractable epilepsies.

Patients and Methods

We performed a retrospective study for the patients who met the following inclusion criteria; (1) who were followed up for more than one year at Samsung Medical Center since the beginning of the RUF use, at the time of 31 Aug 2011, (2) who were less than 19 years of age at the time of the start of RUF treatment, (3) who were classified as intractable epilepsy, meaning presence of persistent seizures despite the use of more than three antiepileptic drugs, and (4) whose data on the clinical characteristics and seizure outcome were available. The data concerning demography, clinical characteristics, seizure-related characteristics, laboratory works including electroencephalography (EEG) and brain magnetic resonance imaging (MRI), and treatment outcome were collected. We conformed to the

classification of the international league against epilepsy (ILAE) in 1981 and 1989 in classifying the seizure and epilepsy of the patients.[4,5]

The efficacy of RUF was evaluated by the response rate, by comparing the seizure frequencies at the baseline and in the last three months. Patients who showed seizure reduction of more than 50% in frequency was defined as responders. The retention rate was another index of efficacy and was defined by the portion of patients who continued with RUF treatment for one year.

Tolerability was evaluated by the presence of side effects. Additionally, we investigated the influencing factors for the response rate or retention rate. SPSS software (version 18.0, SPSS Inc., Chicago, IL, USA) was used in the analysis of nonparametric measures and statistical evaluation was performed by means of chi-square test.

Results

Characteristics of the patients and dose of RUF

Thirty seven patients (27 male, 10 female) were included in this study. Mean age of seizure onset was 32.7±20 months. The mean age at prescription of RUF was 10.5±2.5 (1.8-18.4) years. The etiology of epilepsy, epilepsy syndrome classification, type of seizures, number of prior and concurrent AEDs and other treatment are presented on Table 1 and 2.

The patients were taking many concurrent AEDs (mean=3.9, range: 1-8); valproic acid (n=26), clobazam (n=19), topiramate (n=15), levetiracetam (n=13), lamotrigine (n=13), etc.

Initial starting dose of RUF was mean 7.8 (2.6-31.5) mg/kg/day, and the final maintenance dose was mean 31.4 (6.1-65.6) mg/kg/day. The mean duration of RUF therapy was 10.5±2.73 months and RUF was discontinued in 17 of 37 patients after a mean period of 5.6 (0.6-15.7) months.

Table 1. Demographic and clinical characteristics of the patients (n=37)

	Number of patients (%)
Epilepsy Etiology	
Symptomatic	17 (45.9)
Cryptogenic	20 (54.0)
Epilepsy syndrome	
Generalized epilepsy	16 (43.2)
Lennox-Gastaut syndrome	10 (27.0)
Localization–related epilepsy	9 (24.3)
GE+LRE	1 (2.7)
Infantile spasm	1 (2.7)
Seizure type	
Tonic-clonic seizure	26 (70.2)
Atonic seizure	18 (48.6)
Complex partial seizure	13 (35.1)
Myoclonic seizure	11 (29.7)
Spasm	3 (8.1)
Treatment	Number of AEDs
Number of AED prior to RUF	7.3±1.14 (4-13)
Number of concurrent AED	3.9±0.8 (1-8)
Ketogenic diet prior to RUF	12 (32.4)

RUF, rufinamide; AED, antiepileptic drug.

Efficacy

Response rate

The overall response rate of RUF was 21.6%. The change of seizure frequency according to etiology, types of seizure and epilepsy syndrome is presented in Table 4. Response rates in patients with the atonic seizure type were higher than other seizure types but there were no statistical difference (Table 3).

Retention rate

The overall retention rate of RUF at one year was 54% (20/37 patients). The reasons of discontinuation were ineffectiveness (n=11, 64.7%), adverse effects (n=3, 17.6%), both ineffectiveness

Table 2. Etiology of symptomatic epilepsies (n=17)

Etiology	Number of patients
Neonatal encephalopathy	2
Tuberous sclerosis complex	2
Malformation of cortical development	2
Central nervous system. infection	2
Post traumatic lesion	2
Mitochondrial disease	1
Idiopathic microcephaly	1
Hypoxic-ischemic encephalopathy	1
Cerebrovascular accident	1
Hippocampal sclerosis	1
Chemotherapy induced leukoencephalopathy	1
Nonspecific brain atrophy & developmental delay	1

Table 3. Response to RUF according to the seizure types

Type of seizure	Number of responders (%)
Atonic seizure	5/18 (27.8)
Myoclonic seizure	2/11 (18.2)
Tonic, clonic or tonic-clonic seizure	4/26 (15.4)
Complex partial seizure	1/13 (7.7)

Table 4. Efficacy of RUF according to the etiology, epilepsy syndrome and type of seizure

	N	SF	≥50%	<50%	UC	Inc.	Response rate (%)
Etiology							
Symptomatic	17	0	4	6	7	0	4/17 (23.5)
Cryptogenic	20	2	2	5	9	2	4/20 (20.0)
Epilepsy syndrome							
LGS	10	0	3	2	5	0	3/10 (30.0)
LRE	9	1	1	3	4	0	2/9 (22.2)
GE	16	1	2	6	6	1	3/16 (18.7)
IS	1	0	0	0	1	0	0 (0)
LRE+GE	1	0	0	0	0	1	0 (0)
Type of seizure							
Generalized seizure	23	1	5	6	10	1	6/23 (26.1)
Partial seizure	8	1	1	2	4	0	2/8 (25.0)
①+②	6	0	0	3	2	1	2/6 (33.3)

SF, seizure free; UC, unchanged seizure frequency; Inc.: increased seizure frequency; LGS, Lennox-Gastaut syndrome; LRE, Localization–related epilepsy; GE, Generalized epilepsy; IS, Infantile spasm;

and adverse effects (n=1, 9.8%), and increased seizure frequency (n=2, 11.7%).

The reasons for retention were as follows: responders (n=8, including two seizure free patients, including additive effect with other AEDs <n=2>), good initial response (n=7), improved cognitive function by parent's record (n=2), RUF being more effective than other previous AEDs (n=3). Of non-responders (n=12, 60%), seven patients showed a good initial response to RUF and two patients improved their cognitive abilities and increased their appropriateness by parent's record. The rest of three non-responders were able to decrease other AEDs due to adjunctive treatment with RUF. Two patients, one with seizure free outcome and the other with ≥50% in seizure reduction, were presumed to have additive effect with other AEDs. Furthermore, five patients showed great improvement in specific types of seizures (Atonic seizure type <n=2>, generalized tonic seizure type <n=1>, both <n=2>).

Tolerability

Adverse effects were reported in ten patients (27%): insomnia (n=3), loss of appetite (n=3), somnolence (n=2), irritability (n=2), vomiting (n=1), and dizziness (n=1). There was no life-threatening adverse event related to RUF.

Four patients discontinued RUF due to adverse effects (vomiting, insomnia, dizziness, loss of appetite, respectively) and six patients continued with RUF. Five of them gradually decreased the dose of RUF. One patient maintained RUF because insomnia was mild and tolerable.

Discussion

RUF has established its efficacy in LGS and has been approved as an adjunctive treatment for patients older than four years of age with LGS.[6] In previous studies, RUF was also efficacious and well tolerated in treatment of various epilepsy syndromes other than LGS, including cases of refractory epilepsy in pediatric patients.[3] However, the data about the efficacy of RUF in epilepsies other than LGS are limited.[3,7] In this study, RUF showed a response rate of 21.6% in patients with LGS, intractable GE or LRE. Two patients were found to be seizure free. The retention rate at one year was 54% and a fourth of the patients showed various adverse effects.

The response rate of RUF in patients with refractory epilepsies including LGS was reported to be 26.7-46.7%.[1,3,7,8] Those studies included both child and adult patients and the mean age ranged from 1 to 50 years. According to the study of Kluger *et al*,[7] which was conducted in 60 patients (45 children and 15 adults) treated with RUF over the mean period of 14.5 months with inadequately controlled epilepsy syndromes (range: 3-18 months), the overall response rate was 26.7%. In another study, the patients with refractory epilepsies showed the response rate of 46% at 21 weeks of RUF therapy.[8] This study included pediatric patients with LGS or other intractable epilepsy and the mean age of the patients was 9.5 years in the range of 1-20 years. The response rate of the present study was 21.6% and it is slightly lower than previous studies mentioned above. This difference may result from the intractability of study population including the patients with LGS and highly

intractable generalized epilepsy and localization related epilepsy. At the time of introduction of RUF, the patients had taken a mean 7.2 (range: 4-13) AEDs, which was much higher than the studies of Kluger *et al*. and Joseph *et al*.[7,8]

In our study, patients with LGS showed a slightly higher response rate of 30% than patients with other intractable GE or LRE. In one prospective study with 43 patients with LGS, the overall response rate of RUF at 12 months was 60.5% without worsening of seizures.[2] In another study involving children and young adults with LGS, the response rate was 54.8%.[3] In those studies, patients with LGS took a large part of the total number of patients compared to our study group. Due to such reason, response rate in other studies were higher than the present study. However, RUF was found to be more efficacious in patients with LGS than those with intractable GE or LRE.

As for seizure types, the highest response rate was shown in atonic seizure (27.8%). According to previous data, atonic seizure and tonic seizure were the most improved types of seizure by RUF as adjunctive therapy (63.6% and 48.6%, respectively).[1,9] Also, in a long-term, open-label extension study, 124 patients with LGS (aged 4-37 years) were treated with RUF for a median of 432 days. During the treatment, 47.9% of patients had ≥50% reduction in the frequency of tonic-atonic seizures.[6] Based on previous studies, RUF appeared to be an effective adjunctive therapy for intractable atonic seizures. In our study, partial seizure responded equally to RUF, and a similar result was reported in other studies.[3,7]

Retention rate is known as an indicator for evaluating both efficacy and adverse effects.[10] According to one previous study, the retention rate of RUF at 14.5 months was 41.7%,[7] which is consistent with the present study. In this study, the reasons for retention varied and 60% of them were non-responders (less than 50% in seizure reduction). The reasons for retention in those non-responders were as follows: excellent initial response, definite cognitive improvement by parent's record and RUF being more effective than other previous AEDs.

Coppola *et al*[1] reported early effectiveness of RUF in refractory childhood epileptic encephalopathy patients with or without VPA. Similarly, in our study, seven patients showed a good initial response to RUF during titration.

In our study, two patients reported noticeable improvement in cognitive function even though seizure reduction was less than 50%. One study suggested that RUF has a favorable cognitive profile, increasing its appropriateness for many patients, especially those with cognitive impairment. Their cognitive ability was rather improved in the seizure free-state and no worsening had been reported.[11]

In our study, 27% of patients reported a mild to moderate degree of adverse effects. The most commonly observed adverse events were insomnia (n=3), loss of appetite (n=3) somnolence (n=2), irritability (n=2), vomiting and dizziness. None of previous studies have reported life-threatening adverse effects.[3,7,8] The previous studies reported that vomiting and drowsiness were major symptoms of adverse effects.[3,12] In our study, most adverse events, such as insomnia and loss of appetite, were mild to moderate in severity.

Conclusions

Children with LGS and other intractable epilepsy syndromes showed 21.6% response rate and 54% retention rate during RUF treatment. Also, 27% of children showed adverse effects of RUF and 10.8% children stopped RUF due to adverse effects. The present data suggest that RUF provides good efficacy and tolerability in pediatric patients with refractory generalized or localization related epilepsy syndromes as well as LGS.

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