FULL-LENGTH ORIGINAL RESEARCH

Safety and retention rate of rufinamide in 300 patients: A single pediatric epilepsy center experience

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Summary

Objective: Reports of studies evaluating rufinamide as an add-on therapy in children and adolescents with refractory epilepsy are restricted to a few publications. Prospective multicenter studies including children and adults have yielded important information about several types of epilepsies and syndromes. We evaluated the use of rufinamide in a single pediatric center with a large cohort and long-term follow-up period.

Methods: We retrospectively included patients taking rufinamide from November 2008 to March 2013. Response was defined by a seizure reduction of ≥50% compared to baseline.

Results: Three hundred patients with a median age of 9.1 years (range 0.4–29.6 years) were reviewed. Median follow-up was 9 months (range 1–37 months). Epilepsy etiology was classified as genetic (23.7%), structural/metabolic (41%), and unknown cause (35.3%). Overall, rufinamide treatment led to a median seizure frequency reduction of 59.2% from responders to baseline. Seizure reduction was greater in patients with genetic etiology compared to structural/metabolic (66.2% vs. 45.5% responders, $p = 0.005$). Rufinamide was discontinued in 110 (36.7%) of 300 patients: 63 (21%) due to unsatisfactory response, 47 (15.7%) due to side effects, and in 18 (6%) of those due to both. Most common adverse effects were sleepiness, vomiting, mood changes, nausea, and loss of appetite. Median time to loss of efficacy was 11.6 months (range 3–28 months).

Significance: Rufinamide provides satisfactory seizure reduction as an adjunctive treatment in refractory epilepsy. Results need to be interpreted in the setting of data acquisition, including inherent biases of retrospective studies. Patients with a known genetic etiology may have better responses than patients with structural/metabolic etiology.

KEY WORDS: Epilepsy, Refractory epilepsy, Pediatric, Retention rate, Follow-up, Rufinamide.

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Rufinamide is a triazole derivative that is structurally distinct compared to currently marketed antiepileptic medications. In vitro studies suggest that the antiepileptic efficacy of rufinamide is related to its modulation of sodium channels with prolongation of inactive state.[1] Rufinamide received the status of an orphan drug for epilepsy in 2004 in Europe. It was approved in 2008 by the U.S. Food and Drug Administration (FDA) as an adjunctive medication for the treatment of seizures in the setting of Lennox-Gastaut syndrome (LGS) in patients 4 years and older.[2]

Rufinamide is well absorbed after oral administrations, with no effect from the patient's age or sex, and no effect of single-dose versus multiple-dose administration on steady state. Absorption >85% was described after oral administration of 600 mg with mainly renal excretion (85%), after a mean half-life (T½) of 9 h. At that time, the main metabolite carboxylic acid derivative CGP 47292[3] was pharmacologically inactive, and no utilization of the cytochrome P450 (CYP) route was noted. Analysis of pharmacokinetic and clearance of creatinine using an average concentration at steady state is small when rufinamide is associated with other antiepileptic drugs (AEDs), such as carbamazepine, lamotrigine, phenobarbital, phenytoin, topiramate, and valproate.[4]

A retrospective study with 51 children in the use of rufinamide as an add-on therapy observed that younger children (0–4.9 years) with concomitant use of valproate presented low clearance of creatinine. Analysis of the use of rufinamide concomitant with enzyme-inducing AEDs and valproate demonstrated that patients using an enzyme-inducing AED antiepileptic drug no associate to use of valproate presented an increase of clearance of creatinine higher than threefold in comparison to older children (above 5 years); this was also higher when comparing enzyme inducers with non–enzyme inducers.[5]

A placebo-controlled study of 74 patients with LGS showed that rufinamide led to significant overall seizure reduction and also lowered morbidity in LGS by minimizing drop seizures. This study also maintained a 41% retention rate in this subset of patients in a long-term follow-up of childhood-onset refractory epilepsy.[6–8] Since then, rufinamide has been further investigated for the treatment of other pediatric seizure types.[6,9,10] In addition, rufinamide may be efficacious and safe in epileptic syndromes other than LGS. Previously published series of children with refractory focal and generalized epilepsy as well as epileptic spasms[11–13] suggest that rufinamide is effective in patients with a wide variety of epilepsies.

A summary of the current published studies of rufinamide including pediatric population is included in Table 1. Despite growing evidence that supports the efficacy of rufinamide in the broader pediatric epilepsy setting, there are only few prospective randomized studies that include a high number of patients and long-term follow-up.[7,8,12] The majority of studies report short follow-up periods, mostly ranging from 28 days to 14.5 months, with an average follow-up duration of 6 months.[6–9,11–26]

The purpose of this study is to report our experience with rufinamide in a larger pediatric population from a single center over a longer follow-up period, specifically looking into safety, side effects, and retention rate. In addition, we aim to determine which subgroups in our diverse epilepsy population had a better response rate, as well as identify other predictors for a favorable response. Lastly, we describe the range of side effects experienced by our population and reasons for discontinuation.

Methods

Patient selection

This study was approved by the Boston Children's Hospital Institutional Review Board. We performed a retrospective chart review of all patients <30 years old treated with rufinamide for epileptic seizures from November 2008 to March 2013 at Boston Children's Hospital. Older patients were included if their seizures began in childhood and they had ongoing follow-up at this pediatric epilepsy center. Patients were identified using the Informatics for Integrating Biology and the Bedside software (Partners Healthcare, https://www.i2b2.org/) and Clinical Text Search of the electronic medical record, using the search terms "rufinamide" and "Banzel." Outpatient and inpatient visits, demographic data, seizure characteristics, and neurophysiology and neuroimaging reports were reviewed using a standardized data acquisition tool (details outlined in "Data collection and analysis"). Details regarding rufinamide use, including dose, adverse effects, and number of combinations with other antiepileptic drugs were reviewed. A total of 300 patients from our center had sufficient follow-up seizure data after taking rufinamide for at least 1 month.

Epilepsy classification and seizure control

Epilepsy and seizure types were classified according to the most recent classification update of the International League Against Epilepsy (ILAE) classification.[27] Seizure response was based on the baseline seizure frequency during the 3 months prior to introduction of rufinamide. At the time of the last follow-up, patients were considered responders when seizure reduction was ≥50% compared to baseline seizure frequency. All seizure types were taken into account when assessing these numbers. Tolerability and safety were assessed based on adverse events reported by patients, parents, caretakers, and physicians. Predicting factors for better response to rufinamide were also assessed.

Data collection and analysis

Study data were collected and managed using the REDCap electronic data capture tool.[28] We analyzed the number of responders at last follow-up and calculated percentages in seizure frequency change as compared to baseline. To

Table 1. Clinical studies conducted with rufinamide in the pediatric population

Authors	Study design	N	Age (range)	Seizure type	Seizure reduction (>50%)	Discontinuation rate (%)/adverse events (%)	Follow-up
Glauser et al.[14] (abstract)	Randomized, double-blind, p-c	268	4–16 years	Uncontrolled PS	27.2% vs. 18.3%	DR (7.4%); AE (19.1%) Not specified	0.9 months
Glauser et al.[6]	Randomized, multicenter, double-blind, p-c	139	4–30 years	LGS	32.7% vs. 11.7%	DR (13.5%); AE (55.4%) Vomiting; somnolence and rash	2.8 months
Brodie et al.[9]	Randomized, multicenter, double-blind, p-c	313	M 35.8 years (16–72 years)	PS	28.2% vs. 18.6%	DR (23%); AE (13.5%) Headache; dizziness; somnolence; diplopia; ataxia; seizures; impaired concentration	3 months
Cantarin et al.[15] (abstract)	Prospective, open label	25	<18 years	LGS and other EE	48%	DR (20%); AE (72%) AE mild and transient	8 months (3–18 months)
Nakken et al.[16] (abstract)	Prospective, open label	19	Median 10.9 years (4–17 years)	LGS and LGS-like conditions	11%	DR (36.8%); AE (42%) Seizures	9 months (0.2–13 months)
Ryzi et al.[17] (abstract)	Retrospective	9	5–18	LGS	22%	DR (55.5%); AE (22.2%) Somnolence; dysorexia	3 months
Wiemer-Kruel et al.[18] (abstract)	Prospective	11	5–17.5 years	LGS	18%	DR (36.4%); AE (36.4%) Fatigue; reduce strength; impulse	5–8 months
Kluger et al.[32]	Retrospective	60	1–50 years	LGS, IGES, CGE, PE	46.7%	DR (13.3%); AE (58.3%) Depression, fatigue and vomiting	4 months
Kluger et al.[8]	Randomized, multicenter, double-blind, p-c,	124	4–37 years	LGS	41%	DR (66.1%); AE (70.2%) Rash, vomiting, anorexia, somnolence	14.4 months (0.3–38.3 months)
Kluger et al.[7]	Prospective, multicenter	60	1–50 years	Childhood-onset refractory epilepsy	26.7%	DR (50.9%); AE (61.7%) Fatigue; vomiting; lack of appetite	14.5 months (3–18 months)
Mahendrakar et al.[19] (abstract)	Retrospective	15	Median 17.4 years (10–21 years)	Drug resistant epilepsy 13 (86%) LGS	33%	DR (40%); AE (not specified %) Seizures; behavioral problems	6.4 months
Vendrame et al.[11]	Retrospective	77	Median 12 years (1–27 years)	Partial and generalized epilepsy syndromes	81.1%-Focal cryptogenic; 48.6%-T/A; 46.7%-P	DR (13%); AE (9%) Seizures; drowsiness; rash; headache; loss of vision	4.4 months (1–10 months)
Biton et al.[20]	Randomized, multicenter, double-blind, p-c	357	12–77 years, 15 (8.5%) <18 years (control)	Partial-onset seizure	32.5% vs. 14.3%	DR (15.8%); AE (12.2%) Dizziness; diplopia; convulsion; headache; nausea; vomiting; somnolence; rash	3.2 months
Coppola et al.[21]	Prospective, multicenter, open-label	38	M 13.7 ± 8.3 (4–34 years)	Different childhood-onset refractory EE	39.5%	DR (18%); AE (28.9%) Seizures; vomiting	11.4 months (3–26 months)

Continued

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Table 1. Continued.

Authors	Study design	N	Age (range)	Seizure type	Seizure reduction (>50%)	Discontinuation rate (%)/adverse events (%)	Follow-up
Kim et al.[22]	Prospective open-label	128	M 9.4 ± 4.7 (1.8–19.9 years)	LGS	31.7%	DR (12.5%); AE (32.8%) Fatigue; vomiting; menorrhagia; eye blinking	3.7 months
Olson et al.[13,a]	Retrospective	38	Median 7 years (17–23 months)	Epileptic spasms	53%	DR (15%); AE (8.6%) Seizures; decrease of appetite; sedation;	5.7 months (0.3–13.6 months)
Vendrame et al.[23,a]	Retrospective	5	M 2.6 years (25–41 months)	MMPEI	40%	DR (60%); AE (20%) Vomiting	6–7 months
Hausler et al.[24]	Retrospective	3	M 3.3(2.5–3.3 years)	Epilepsy with myoclonic absences	100% 66.7% – seizure-free	DR (0%); AE (0%)	12 months (0.5–24 months)
Mueller et al.[26]	Retrospective	20	M 12.2 years (3–23 years)	Dravet syndrome	6 months – 20% 18 months – 5%	DR – 6 months (65%)/ 18 months (85%); AE (10%) Seizures; gait disorders; decrease of appetite; nausea; abdominal pain; behavioral changes	5.3 months (9 days to 34 months)
von Stulpnagel et al.[25]	Retrospective	8	M 33.5 months (22–52 months)	Myoclonic-astatic epilepsy		DR-6 months (25%)/ 12 months (87.5%); AE (25%) Sleepiness; decrease of appetite	12 months (2–18 months)
Moavero et al.[12]	Prospective, multicenter, open-label	70	M 10.7 (3–21 years)	Focal resistant epilepsy	38.57%	DR (8.5%); AE (24.3%) Seizures; vomiting; behavioral disturbance	12 months

AD, adverse event; CGE, cryptogenic generalized epilepsy; DR, discontinuation rate; EE, epileptic encephalopathies; IGES, idiopathic generalized epilepsy syndromes; LGS, Lennox-Gastaut syndrome; M, mean; MMPEI, malignant partial epilepsy of infancy; PE, partial epilepsy; PS, partial seizure; p-c, placebo-controlled.

[a]Described only AE, which led to discontinuation.

[a]Four of the five patients published in Vendrame et al.[23] and 28 of the 38 patients published in Olson et al.[13] are included in this sample.

search for predictors of response to rufinamide, a binary logistic regression (backward modeling) was performed with response to rufinamide (≥50% seizure control at last follow-up vs. nonresponder) as dichotomous outcome variable. Age at baseline, gender, age at epilepsy onset, duration of epilepsy, dose at first follow-up, and etiology were chosen as predictor variables on the grounds of previous research, clinical implications, and preliminary data analysis. SPSS Version 21(SPSS Inc., Chicago, IL, U.S.A.) was used to perform statistical analyses. Kaplan-Meier survival analysis was used to estimate the cumulative probability of discontinuation of rufinamide. Time to event was defined as the duration from introduction of rufinamide until discontinuation due to adverse effects or inefficacy. Interval observations were censored when (1) patients continued on rufinamide, or (2) patients dropped out due to noncompliance or missing follow-up. Because most published data on the use of rufinamide is in the >4 age group, a secondary analysis was done investigating outcomes specifically in children ≤4 years.

Results

Demographics

A total of 356 patients younger than the age of 30 were prescribed rufinamide for the treatment of epilepsy over the time period under study. Fifty-six patients had incomplete data or did not meet the study criteria (Fig. 1). Three-hundred patients were included (141 [47.0%] girls), and the median age was 9.1 years (interquartile range [IQR] 4–14.6; range 0.4–29.6). Epilepsy etiology, seizure type, comorbidities, concomitant antiepileptic drugs, electroencephalography (EEG) characteristics and imaging are presented in Table 2. In our sample, 127 (42.3%) of 300 patients presented with lesions on magnetic resonance imaging (MRI), and 49 (38.6%) of these patients had focal epilepsy as determined by ictal EEG. Of these, 46 (93.9%) patients had diffuse lesions and 2 (4.1%) of 49 had focal lesions. None of the 127 patients with lesional MRI were eligible for a surgical procedure at the time of initiation of rufinamide. Patients had tried a median of 6 (IQR 5–8; range 1–15) AEDs before using rufinamide. Two hundred ninety-three patients (97.7%) were receiving concomitant antiepileptic drugs: 46 patients (15.3%) were taking one additional medication, 75 patients (25.0%) were taking two additional medications, 91 patients (30.3%) were taking three additional medications, and 81 patients (27.0%) were taking more than three additional epilepsy medications (maximally five). Ninety-eight patients (32.7%) were taking valproate, 15 of 98 patients (15.3%) were taking an enzyme-inducing AED (phenobarbital, phenytoin, carbamazepine, and oxcarbazepine) and 83 (84.7%) of 98 were taking a non–enzyme-inducing AED. The median follow-up duration was 11.7 months (IQR 3–19 months; range 1–37). Loss of efficacy was observed with a median of 11.6 months (IQR 6–16; range 3–28). Ten percent (30/300) of our patients had LGS.

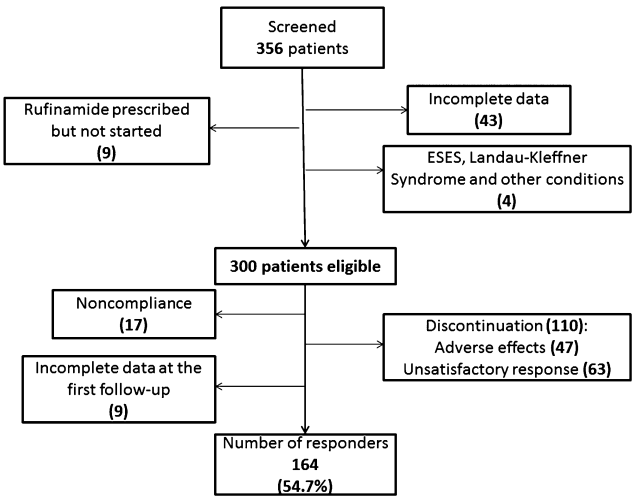

Figure 1.
Rufinamide was prescribed in 356 patients, and we excluded a total of 56 patients. Forty-three patients were excluded due to incomplete data. In nine patients rufinamide was prescribed but not started, and four patients had electric status epilepticus during sleep (ESES), Landau-Kleffner syndrome, and other conditions. Therefore, three hundred patients were included.

Overall seizure outcome

Median seizure reduction was 59.2%. One hundred sixty-four patients (54.7%) had ≥50% seizure reduction and 42 300 (14%) were seizure-free at the last follow-up (detailed outcome data are presented in Table 3). Using a logistic regression model, we found that patients with genetic etiology were more likely to become responders (66.2%) as compared to patients with structural/metabolic etiology (45.5%; p = 0.005). Patients with *SCN1A* mutation did not present with a good response: only one of four patients presented seizure reduction ≥50%. Of our 30 patients with LGS, 19 (63.3%) obtained a ≥50% seizure reduction.

In addition, a higher dose of rufinamide at first follow-up was indicative of better response at last follow-up (responders: mean 29.6 ± (Standard deviation) 18.3 mg/kg/day; nonresponders: mean 25.0 ± 17.5 mg/kg/day, p = 0.004). The odds ratio for patients with higher doses of rufinamide was 1.6 times (95% confidence interval [CI] 0.95–2.87) compared to patients with lower doses of the medication (details for specific etiology in Table S1).

Comedication

When comparing the number of AEDs at baseline and last follow-up, 195 patients (65%) were taking the same number of comedications, 47 patients (15.7%) were taking additional AEDs (maximum three), and 58 patients (19.3%)

Table 2. Demographic and clinical data

Characteristics	Values, n (%)
Girls	141 (47)
Mean age, years (SD; range)	9.8 (6.6; 0.4–29.6)
Epilepsy etiology	
Genetic	71 (23.7)
Structural/metabolic	123 (41)
Unknown	106 (35.3)
Specific epilepsy etiology	
Hypoxic ischemic encephalopathy	34 (11.3)
Neurocutaneous syndrome (other than tuberous sclerosis)	4 (1.3)
Stroke/hemorrhage	10 (3.3)
Inborn error of metabolism	8 (2.7)
Developmental encephalopathy	12 (4)
Malformation of cortical development	43 (14.3)
Neoplasm	8 (2.7)
Genetic	71 (23.7)
Encephalitis	8 (2.7)
Tuberous sclerosis complex	7 (2.3)
CNS infection	3 (1)
Unknown	93 (31)
Seizure type[a] in visit before introduction of rufinamide	
Generalized tonic–clonic	92 (30.7)
Generalized absence (typical and atypical)	45 (15)
Generalized myoclonic	65 (21.7)
Generalized clonic	9 (3)
Generalized tonic	122 (40.7)
Astatic	38 (12.7)
Focal	89 (29.7)
Unknown	37 (12.3)
Epileptic spasms	54 (18)
Clinical exam[a]	
Normal	91 (30.3)
Quadriplegia	82 (27.3)
Diplegia	12 (4)
Hemiplegia	27 (9)
Monoplegia	6 (2)
Hypotonia	75 (25)
Extrapyramidal	13 (4.3)
Cranial nerve abnormalities	12 (4)
Comorbidities[a]	
Autism	38 (12.7)
Mood disorders	6 (2)
Neurobehavioral disorders	32 (10.7)
Intellectual and developmental disabilities	231 (77)
MRI results	
Lesional	127 (55.5)
Nonlesional	102 (44.5)
EEG[a]	
Normal	30 (10.0)
Generalized slowing	89 (29.7)
Focal slowing	38 (12.7)
Asymmetric slowing	14 (4.7)
Generalized epileptiform discharges	67 (22.3)
Focal epileptiform discharges	73 (24.3)
Multifocal	151 (50.3)
Lateralized periodic discharges	1 (0.3)
Rufinamide dose (mg/kg/day)	
Start dose (mean; range)	8.8; 0.9–52.6
Final dose (mean; range)	39.5; 1.8–135
Concomitant antiepileptic drugs	
One AED: 46; two AEDs: 75; three AEDs: 91; >3 AEDs: 81	
Levetiracetam	135 (45)
Valproate	98 (32.7)
Diazepam	89 (29.7)
Lamotrigine	77 (25.7)
Clonazepam	68 (22.7)
Topiramate	63 (21)
Lorazepam	47 (15.7)
Clobazam	44 (14.7)
Oxcarbazepine	28 (9.3)
Phenobarbital	23 (7.7)
Vigabatrin	16 (5.3)
Phenytoin	15 (5)
Gabapentin	13 (4.3)
Lacosamide	11 (3.7)
Clorazepate	8 (2.7)
Ethosuximide	6 (2)
Nitrazepam	6 (2)
Pregabalin	4 (1.3)
Primidone	3 (1)
Felbamate	3 (1)
Bromide	1 (0.3)
Methsuximide	1 (0.3)

[a]Patients can be in more than one category.

were taking fewer AEDs (maximum three) at last follow-up. There was no significant difference between responders versus nonresponders. There was also no relationship in responders rate among the 97 (32.2%) patients who were taking VPA at last follow-up. Of these 97 patients, 12 (12.2%) were also taking an enzyme-inducing AED as comedication (valproate), and 83 (86%) patients were taking a non–enzyme-inducing AED (carbamazepine, phenobarbital, phenytoin, oxcarbazepine, and lamotrigine). Of the 203 patients who were not taking valproate at last follow-up, 52 (25.6%) were taking an enzyme-inducing AED as comedication, and 191 (94%) were taking a non–enzyme-inducing AED. In both groups (valproate vs. no valproate), the intake of enzyme-inducing AEDs did not significantly affect the response to use of rufinamide (Fisher's exact test).

Adverse effects

Adverse effects were observed in 79 (26.3%) of 300 patients. The most common adverse effects were sleepiness in 21 (26.6%), vomiting in 17 (21.5%), mood changes in 13 (16.5%), nausea in 9 (11.4%), and loss of appetite in 9 (11.4%) patients. Other adverse events observed less frequently included rash in 7 (8.9%), dizziness in 6 (7.6%), and loss of coordination in 6 (7.6%) patients. Fifty-six patients (70.9%) presented with one side effect, 19 (24.1%) with two, and 4 (5%) with three. All side effects were observed during introduction and titration period.

Table 3. Outcome of rufinamide treatment

Total number	300
Patients <21 years	282 (94%)
Median age (IQR)	9.1 years (4–14.6)
Mean follow-up (IQR)	11.7 months (3–19)

Overall outcome N	Median % seizure reduction	N (%) of responders
Response	59.2% (0.0%, 92.2%)	164 (54.7)

General etiology	N	Median % seizure reduction	N (%) of responders	χ^2 test
Genetic	71	66.7% (16.7%, 95.6%)	47 (66.2)	$\chi^2_1 = 7.7$ $p = 0.005$
Structural/ metabolic	123	40% (0%, 91.7%)	56 (45.5)	
Unknown	106	62.5% (0.0%, 91.3%)	61 (57.5)	

Discontinuation

One-hundred ten patients (36.7%) discontinued treatment during the follow-up period. Reasons for discontinuation included adverse events in 47 (15.7%), unsatisfactory response in 63 (21%), and a combination of both in 18 (6%) patients. Early side effects observed within the first month of initiation occurred at a rate of 26.3%. No relationship was observed between discontinuation and number of AEDs in use, as well as use of valproic acid or titration mode of rufinamide. Discontinuation due to adverse effects occurred within the first 3 months (n = 29).

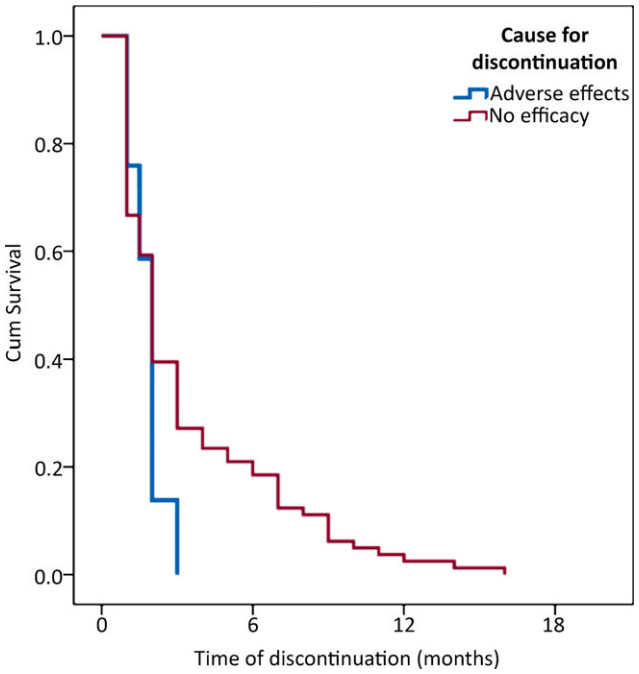

Figure 2.
Discontinuation due to inefficacy occurs over a longer time span (red graph) as compared to discontinuation due to adverse events (blue graph; n = 110; log rank test: p = 0.018).
Epilepsia © ILAE

Discontinuation due to inefficacy (including patients with inefficacy and adverse events) occurs over a longer time span, up to 16 months compared to discontinuation due to adverse events (n = 110; log rank test: p = 0.018; Fig. 2). Seventeen patients discontinued treatment due to noncompliance (5.7%). The most frequent side effects leading to discontinuation were gastrointestinal symptoms (nausea, vomiting, and stomach pain) in 15 (31.9%) of 47, excessive sleepiness in 12 (25.5%) of 47, rash in 5 (10.6%) of 47, dizziness in 5 (10.6%) of 47, and loss of appetite in 5 (10.6%) of 47 patients. Thirty-two (40.5%) of 79 patients experienced only minor adverse effects, which did not result in discontinuation.

Retention rate in patients younger than 4 years of age

In 73 patients (24.3%) younger than 4 years (43 male, median age 2.3 years), the response rate was 53.4% (39 of 73). Patients younger than 4 were distributed according to age, as follows: (1) <1 year, 2 patients (2.7%); (2) 1–1.9 years, 28 (38.2%); (3) 2–2.9 years, 21 (28.8%); and (4) 3–4 years, 22 (30%).

The overall seizure frequency decreased significantly as compared to baseline (median 53.3%; IQR 0%, 95.9%, p < 0.001), with 14 out of 73 patients (19.2%) becoming seizure-free. In addition, we analyzed patients with epileptic spasms (ES), a syndrome that occurs in the first year of life (90%), with peak incidence between 3 and 7 months, and also after 18 months of age. Patients with ES (37%), including late-onset epileptic spasms, were compared with other types of seizures (generalized and partial, 63%); no statistically significant difference in response was observed (Table 4). In this subgroup, adverse effects were observed in 12 (16.4%) of 73 patients, and 9 (12.3%) of 73 of these led to treatment discontinuation.

Epileptic spasms were observed in 27 patients, in 6 (22.2%) due to genetic etiology, 13 (48.2%) due to structural/metabolic etiology, and 8 (29.6%) due to unknown causes. Although all six patients with genetic etiology were

Table 4. Outcomes for patients <4 years of age

Total number	73

Characteristics	Values, n (%)
Males	43 (58.9)
Median age (IQR)	2.3 years (1.7–3.2)
Median follow-up (IQR)	8 months (2–18)

Overall outcome N	Median % seizure reduction (IQR)	N (%) of responders
Response	53.3% (0.0%, 95.9%)	39 (53.4)

Seizure type	N	Median % seizure reduction	N (%) of responders
Epileptic spasms	27	75% (0.0%, 91.7%)	16 (59.3)
Generalized epilepsy	35	33.3% (0.0%, 98.7%)	16 (45.7)
Focal epilepsy	11	83.3% (0.0%, 100%)	7 (63.6)

responders, only 6 patients of 13 patients with structural/metabolic etiology showed a response rate of 50% or higher (Fisher's exact test: $p < 0.05$).

Discussion

Summary

We evaluated the retention rate of rufinamide using a retrospective review of a single tertiary pediatric neurology center with a large cohort and longer term follow-up. The overall number of responders was 54.7%, of whom 14% (42 of 300) achieved complete seizure freedom. Discontinuation rate was 36.7% (110 of 300), primarily due to inefficacy and adverse effects. Overall, despite reviewing a diverse and refractory epilepsy population, we found rufinamide to be effective and safe as adjunctive treatment for many types of refractory epilepsy.

Epilepsy outcome

To date, few pediatric studies evaluating the use of rufinamide including in the pediatric population have been published. One large prospective pediatric study followed 268 children, but only for 28 days. The study did therefore not demonstrate the efficacy of rufinamide as an add-on for partial seizures in children over long-term follow-up.[14] Two large multicenter studies, respectively, enrolled 313 and 357 adolescents and adults,[6,20] also with partial seizures and short follow-up. Both demonstrated efficacy of rufinamide in an adult population. Retrospective studies with long-term follow-up of pediatric patients have largely been restricted to small samples and typically one type of epilepsy or seizure. At times, these studies have shown excellent results, as observed in patients with myoclonic absence, with a response rate of 100% and complete seizure control in two (66.7%) of three patients.[24] The majority of available studies evaluated rufinamide outcomes following shorter trial periods, often <1 year.[6,9,11,13–23,26] Few studies have evaluated rufinamide for longer periods of time.[7,8,12,24,25] In our study, we analyzed a large sample of 300 patients from a single pediatric center of epilepsy, with different types of epilepsy with different seizure types. With longer follow-up and greater numbers, we report a more complete assessment of safety of rufinamide and were able to identify factors predictive of retention rate in our population.

A study including refractory childhood epileptic encephalopathies other than LGS observed rates of 39.5% in seizure reduction.[21] Two multicenter randomized placebo-control studies with partial seizures demonstrated a median reduction of 29.3%[9] and 23.3%,[20] respectively. In patients with focal drug-resistant epilepsy, responder rates of 38.6% were reported, with better response in patients with structural/metabolic etiology (42.6%).[12]

Comedications

We did not find a significant difference between the numbers of comedications taken at baseline and at the last follow-up in relationship to the responder rate. The same was observed for the use of valproate in combination with enzyme-inducing or non–enzyme-inducing AEDs. In addition, we did not find a relationship between higher dose during the first follow-up and better responder rate.

Outcomes in LGS

Response rates in children with LGS were higher in our study (63.3%) when compared to previous studies that evaluated rufinamide in LGS, with response rates ranging from 18% to 41%.[6,7,17,18,22] The majority of these studies had a follow-up of <6 months. The only study with a longer follow-up (median 14.5 months) also presented a higher rate of responders.[7] The higher rates in the present study may reflect exclusion of patients from our analysis that had inefficacy and subsequent discontinuation within 1 month. In this population with refractory epilepsy, changes in other drugs or other interventions (e.g., epilepsy surgery) could also contribute to achieving seizure reduction. Although we were not able to perform additional analyses in LGS, the etiology of this syndrome remains heterogeneous. Future studies will need to prospectively analyze some of these conditions in order to provide more information on specific etiologies as a predictive factor for responses to rufinamide.

Predictive factors for seizure reduction

In a study with the majority of patients having *SCN1A* gene mutation, 16 (80%) of 20 demonstrated a seizure increase in one third of the patients after the introduction of rufinamide.[26] This specific epilepsy syndrome occurs due to a mutation in type I sodium channel (Na_v 1.1) caused by de novo loss-of-function mutations in the *SCN1A* gene leading to haploinsufficiency of $Na_V1.1$ channels. In addition, in an animal model (mice), a significant loss of sodium current in hippocampal γ-aminobutyric acid (GABA)ergic inhibitory interneurons was observed.[29] Despite the fact that rufinamide acts in prolonging the inactive state of sodium channels, this study had a low retention rate, leading to the conclusion that rufinamide may not be a good choice for patients with this specific mutation.

We observed the same findings among patients in our smaller sample, where one (25%) of the four patients achieved ≥50% in seizure reduction. So far, there are no other studies comparing the efficacy and safety of rufinamide with another specific genetic etiology.

A higher dose at first follow-up did not present a relationship with an increase of adverse events ($p = 0.484$). Unfortunately there are no published articles that mention the dose at the time of the first follow-up, and it suggests an impact of the medication titration. Specifically, it raises the question of whether rufinamide is best started with a rapid

titration schedule in order to achieve goal levels faster and higher retention rates. In practice, side effects may limit the titration rate in some.

Discontinuation rate and adverse effects

In our series, treatment was discontinued in 36.7%. This was due to adverse effects in 15.7% and to unsatisfactory response to therapy in 21%. The discontinuation rate in both retrospective and prospective studies has been variable (Table 1). In prospective studies, discontinuation rates between 7.4% and 66.6% have been reported.[6,7,9,12,14–16,18,20–22] Rates from retrospective studies were even higher, and ranged from 13% to 87.5%.[8,11,13,17,19,23–26] In contrast, when analyzing adverse events, prospective studies tended to report higher rates. This is likely caused by the information bias in retrospective studies.

In general, rufinamide is well tolerated. Side effects include dizziness, fatigue, nausea, vomiting, diplopia, and somnolence, which are described in our study, and this is in agreement with reports in the literature.[30] In the pediatric population, symptoms of somnolence, vomiting, and headache have also been noted.[31] Side effects may be sufficiently severe to require treatment discontinuation in a substantial percentage of patients, as seen in 15.7% of our patients, and in a comparable percentage in other trials with rufinamide.[9,20,21]

In addition, we observed patients that discontinued the medication due to inefficacy after an extended time frame (range 1–16 months). This observation raises several questions: (1) Was early lack of efficacy inherent to the patient or the epilepsy severity? (2) Is there individual tolerance after a "honeymoon period"? (3) Are we observing the natural evolution of the underlying epilepsy? These are factors and questions raised by the present retrospective analysis that cannot be fully explained. Adverse effects of rufinamide that led to discontinuation occur early, within the first 3 months of treatment. The occurrence of early side effects in 26.3% of patients was similar to values reported in the literature (7.8–72%).[9,11,20] Withdrawal of medication in patients who experience early adverse effects, tolerance to side effects, and optimization of medication dosing may explain the gradual reduction in adverse effects over a more prolonged follow-up.

The findings from this study must be interpreted within the setting of data acquisition, including inherent information and selection bias. In addition, this study includes patients with refractory epilepsy treated with rufinamide as an add-on therapy, which may have confounded results. We were unable to account for the retention rate of other treatments, for example, change in medication, ketogenic diet, and vagus nerve stimulation, applied during the treatment period or for drug interactions. However, this mimics conditions in clinical practice. No control or comparison group was available in this study. Nonetheless, we provide a large series of patients from a pediatric hospital, including patients <4 years of age, with a relatively long follow-up period, and including dosing and subsets of patients with better response with this medication.

Conclusions

Our experience from a large group of patients at a single pediatric tertiary reference hospital suggests that rufinamide provides good seizure reduction as an adjunctive treatment in refractory pediatric epilepsy, with better response in patients with epilepsy of genetic etiology, and possibly in patients with higher initial dosing. In addition, rufinamide appears to have a good safety profile. Our results indicate a broad spectrum of retention rate including focal and generalized epilepsy and epileptic spasms.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Response in genetic and structural/metabolic etiology.