Update on rufinamide in childhood epilepsy

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Abstract: Rufinamide is an orally active, structurally novel compound (1-[(2,6-difluorophenyl)methyl]-1-hydro-1,2,3-triazole-4-carboxamide), which is structurally distinct from other anticonvulsant drugs. It was granted orphan drug status for the adjunctive treatment of Lennox-Gastaut syndrome (LGS) in the United States in 2004, and released for use in Europe in 2007. In January 2009, rufinamide was approved by the United States Food and Drug Administration for treatment of LGS in children 4 years of age and older. It is also approved for adjunctive treatment for partial seizures in adults and adolescents. Rufinamide's efficacy mainly against atonic/tonic seizures in patients with LGS seems nowadays indubitable and has been confirmed both in randomized controlled trial and in open label extension studies. More recently, rufinamide was evaluated for the adjunctive treatment of childhood-onset epileptic encephalopathies and epileptic syndromes other than LGS, including epileptic spasms, multifocal epileptic encephalopathy with spasm/tonic seizures, myoclonic-astatic epilepsy, Dravet syndrome and malignant migrating partial seizures in infancy. This review updates the existing literature data on the efficacy and safety/tolerability of rufinamide in childhood-onset epilepsy syndromes.

Keywords: rufinamide, Lennox-Gastaut syndrome, epileptic encephalopathy, myoclonic-astatic syndrome, Dravet syndrome, malignant migrating partial seizures in infancy, refractory childhood epilepsy

Introduction

Rufinamide is an orally active, structurally novel compound (1-[(2,6-difluorophenyl)methyl]-1-hydro-1,2,3-triazole-4-carboxamide), which is structurally distinct from other antiepileptic drugs (AEDs). In experimental models rufinamide was effective in suppressing neuronal hyper-excitability by prolonging the inactivation of voltage-gated sodium channels.¹ It also showed a broad spectrum of anticonvulsant activity, suppressing maximal electroconvulsive shock-induced seizures in both rats and mice models, and in PTZ-test in mice.² Rufinamide is well absorbed after oral administration, demonstrates low protein binding, and is metabolized by enzymatic hydrolysis without involvement of cytochrome P450 enzymes, conferring a low drug interaction potential.³

It was granted orphan drug status for the adjunctive treatment of Lennox-Gastaut syndrome (LGS) in the United States in 2004, and released for use in Europe in 2007. In January 2009, rufinamide was approved by the United States Food and Drug Administration for treatment of LGS in children 4 years and older. It is also approved for adjunctive treatment for partial seizures in adults and adolescents.⁴

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In 3 randomized controlled trials, rufinamide was effective and safe for the adjunctive treatment of partial seizures in adults and adolescents,^{4,5} and the treatment of generalized seizures associated with LGS.⁶

Until recently, few studies were available on rufinamide for the treatment of epileptic encephalopathies and specific childhood-onset epileptic syndromes other than LGS.^{7–11} The purpose of this review is to report an update of the existing literature data on the efficacy and safety/tolerability of rufinamide in childhood-onset epilepsy syndromes.

Rufinamide and Lennox-Gastaut syndrome

LGS, one of the catastrophic epilepsies of childhood, is classified by the International League against Epilepsy as a symptomatic generalized epilepsy syndrome.¹² It is characterized by the electroclinical features of (1) electroencephalogram (EEG) showing abnormal background, diffuse slow-spike-and-wave complexes (1.5–2.5 Hz), and paroxysmal fast rhythms (10 Hz), although the latter may only occur in sleep; (2) multiple types of epileptic seizures typically including tonic, typical absences, and drop-attacks; some patients may develop myoclonic, generalized tonic-clonic, or partial seizures; and (3) slow mental development and/or behavioral disturbance. Over 75% of children with LGS have an identifiable cause (symptomatic or presumed symptomatic/cryptogenic). These include both congenital and acquired etiologies such as cortical maldevelopment and neuronal migration disorders, perinatal hypoxia/ischemia, infections of the central nervous system, or neurometabolic disorders.

West syndrome is present in the clinical history of about 20% of these patients. LGS is notoriously drug-resistant and 80% to 90% of patients continue having seizures in adult life and nearly all (85%–90%) have severely impaired cognition and behavior, finally requiring to be institutionalized.

Many treatment attempts in LGS are anecdotal and empirical and AED therapy nearly always fails to control seizures completely, although a reduction in seizures, usually temporarily, may be achieved. A rational polytherapy is then the rule, including old and new antiepileptic drugs.

Only one double-blind, randomized, placebo-controlled study is so far available on rufinamide for the treatment of Lennox-Gastaut refractory seizures.⁶ Another three, uncontrolled, open label trials with rufinamide have been published, of which 1 is a long-term, open-label extension study.^{13–15}

The unique randomized controlled trial by Glauser et al⁶ involved 138 patients between ages of four and 30 years

who had LGS diagnoses for a median of 7.5 years. About one-third of participants were under twelve years of age. After a 28-day baseline period, 138 patients received either rufinamide ($n = 74$) or placebo ($n = 64$) in addition to their other AEDs. After a 12-week parallel group treatment (2-week titration, 10-week maintenance), the median percentage reduction in total seizure frequency was greater in the rufinamide therapy group than in the placebo group (32.7% vs 11.7%, $P = 0.0015$), and in tonic-atonic (drop-attack) seizure frequency with rufinamide (42.5% median percentage reduction) vs placebo (1.4% increase). The rufinamide group had a greater improvement in seizure severity ($P = 0.0041$) and a higher 50% responder rate compared with placebo for total seizures ($P = 0.0045$) and tonic-atonic seizures ($P = 0.002$). Tolerability profile of rufinamide was overall favorable with somnolence (24.3% on rufinamide vs 12.5% on placebo) and vomiting (21.6% vs 6.3%), being the most common adverse events.

The long-term efficacy and tolerability of rufinamide in 124 of the 138 patients with LGS who had previously completed a 12-week double-blind study, were reported recently by Kluger et al.¹⁴ During the extension study, the median dose of rufinamide was 1800 mg/day (52.9 mg/kg/day). Overall, patients were treated with rufinamide for a median (range) of 432 (10–1149) days. Rufinamide was added to 1 ($n = 13$), 2 ($n = 69$) or 3 ($n = 42$) concomitant AEDs at the start of the extension phase.

At the time of the study termination, 42 patients (32.9%) were still receiving rufinamide and 82 patients (66.1%) had discontinued due to: poor efficacy ($n = 51$), adverse events ($n = 12$) or other reasons ($n = 19$). During the last 12 months of treatment, 41.0% and 47.9% of patients had $\geq 50\%$ reduction in total and tonic-atonic seizure frequency, respectively. The most common adverse events (AEs) were vomiting (30.6%) and pyrexia (25.8%). It was concluded that rufinamide appeared to be an effective long-term adjunctive therapy for the treatment of the LGS-associated seizures in children and young adults.

Other data come from two European studies,^{13,15} and one published in the US.¹⁶ The first study from Europe,¹³ using observational retrospective data from multiple centers, examined the effectiveness of rufinamide in 45 children and 15 adults with refractory epilepsy, including 31 patients with LGS. After an observation period of 12 weeks, the highest response rate was observed in patients with LGS (17/31, 54.8%) and the lowest in patients with partial epilepsy (4/17; 23.5%). Four of the five seizure-free patients had LGS. For disabling seizure types, the highest responder rates

were observed for tonic seizures (45.0%) and drop-attacks (47.1%). Investigators found fatigue, vomiting and anorexia in 10% to 20% of patients but no serious adverse effects. The results of this study led authors to conclude that the efficacy of rufinamide in patients with generalized epilepsy was comparable to that in patients with LGS, whereas this drug was less effective in patients with partial epilepsy.

In 2010, the first Italian multicenter experience with rufinamide in children and adults with LG syndrome was also reported.¹⁵ In a prospective, add-on, open-label treatment study, 43 patients (26 males), aged between four and 34 years (mean 15.9 ± 7.3 , median 15.0), were treated with rufinamide for a mean period of 12.3 months (range 3–21 months). Twenty patients of 43 were diagnosed as cryptogenic. After a mean follow-up period of 12.3 months (range 3–21 months), the response rate ($\geq 50\%$ decrease in countable seizures) was 60.5% in total, with a final mean dose of rufinamide of 33.5 mg/kg/24 hours (range 1.5–60) if combined with valproic acid, and 54.5 mg/kg/24 hours (range 21.8–85.6) without valproic acid. A 50% to 99% reduction in seizure frequency was experienced by 51.1% and a complete seizure control in the last 4 weeks' follow-up was experienced by 9.3% of patients.

Drop attacks and tonic seizures were most improved by rufinamide adjunctive therapy.

Further data, also encouraging for LGS patients, were more recently reported in a retrospective observational study by Vendrame et al.¹⁶ In 26 patients with LGS out of 91 pediatric patients with a median follow-up of 12 years (range 1–27 years), 38.4% showed a $\geq 50\%$ decrease in seizure frequency, with a maximal responder rate in tonic-atonic and partial seizures. This trial confirmed rufinamide to be particularly effective against drop-attacks and/or tonic seizures in patients with LGS.

Rufinamide and other epileptic encephalopathies

Besides LGS, the epileptic encephalopathies of infancy and early childhood, often defined as catastrophic epilepsies because of the significant cognitive and neurological morbidity not rarely associated with death, comprise very early epileptic encephalopathies, West syndrome, severe myoclonic epilepsy of infancy (Dravet syndrome), refractory myoclonic-astatic epilepsy (Doose syndrome), and the recently recognized syndrome of malignant migrating partial seizure in infancy.

Epileptic (infantile) spasms are the defining clinical manifestation of West syndrome. The symptomatic form of West syndrome is by far the commonest detected cause and

probably accounts for 80% of all cases. Several pre-, peri- and postnatal insults are responsible, ranging from hypoxia-ischemia, infections, trauma, and intracranial hemorrhage to malformations of cortical development, neurocutaneous diseases, genetic and chromosomal abnormalities and, less often, inborn errors of metabolism.

Idiopathic West syndrome, with normal premorbid development and possible hereditary predisposition is far less frequent, accounting for 5% to 30% of all cases.

Treatment options for epileptic spasms are limited¹⁷ and effective treatment of spasm remains an important unmet medical need,¹⁸ as long-term developmental and cognitive outcomes for patients with spasms is likely to be improved with effective control of spasms.

Recently, Olson et al⁸ reported on a retrospective review of their experience with rufinamide as adjunctive therapy in 38 patients with refractory epileptic spasms, aged 17 months to 23 years (median seven years). Rufinamide was added to a median number of three AEDs, at the median starting dose of 9 mg/kg/day (range 2–8), while the median final treatment dose was 39 mg/kg/day (range 8–92).

Median duration of follow-up since starting rufinamide was 171 days (range 10–408). The responder rate, defined as $\geq 50\%$ reduction in spasms, was 53%. Nine patients (24%) achieved a reduction in spasms $\geq 90\%$, and two patients (5%) achieved $\geq 99\%$ reduction in spasms. Rufinamide was discontinued in 7 of 38 patients (18%) because of lack of efficacy, worsening seizures, or other side effects. Minor side effects were reported in 14 of 38 patients (37%), including increased seizure frequency at high dose (5), decreased appetite (3), sedation (3), eyes crossing (1), vomiting (1).

A number of limitations may be stressed in the context of this study: its retrospective nature, the quantification of spasm frequency before and after treatment, essentially based on clinical notes and more rarely on EEG data, and the high refractoriness of patients referred to a tertiary epilepsy center. Furthermore, it must be underlined that 1 patient only had hypsarrhythmia at the time of treatment with rufinamide, and only 9 other patients had a previous history of hypsarrhythmia. The remaining 29 patients had a diagnosis of LGS (10), Ohtahara syndrome (1), unclassified epilepsy (15), and migrating partial seizure in infancy (3). Last, epileptic spasms lasting 1 to 15 seconds seemed more often to be tonic seizures rather than infantile spasms.

In another study by Coppola et al,⁷ rufinamide was assessed for the adjunctive therapy of epileptic encephalopathies and generalized epilepsies other than LGS, including severe multifocal encephalopathy with spasm/tonic seizures,

refractory myoclonic-astatic epilepsy, Dravet syndrome, and malignant migrating partial seizures in infancy. This prospective, open-label study of rufinamide as adjunctive therapy reports a decrease in seizure frequency in seven of the 22 patients (31.8%) with multifocal encephalopathies with spasms and tonic seizures, and in seven of 11 patients (63.8%) with (bi)frontal spike-wave discharges.

Concerning seizure types, this study confirms rufinamide to be particularly effective against drop-attacks and, to a lesser extent, tonic and tonic-clonic seizures. Furthermore, response to rufinamide was less sustained in this kind of encephalopathy than in patients with LGS (40% vs 55% as reported by Glauser et al⁶ and Kluger et al.¹⁴

Kluger et al^{13,14} reported another seven patients with otherwise unclassified cryptogenic or symptomatic generalized epilepsies, and treated with rufinamide. These authors found an unexpectedly high rate of responders in this small group of patients (42.8%), with one patient seizure-free and two with 50%–75% seizure decrease. In the long-term assessment,¹⁹ after 18 months, two of these patients were still on rufinamide and 1 of them was seizure-free.

Myoclonic-astatic epilepsy, also known as Doose syndrome, is a generalized epilepsy syndrome in children aged one to six years which occurs in 1.6% to 4% of all newly diagnosed epilepsies in children and adolescents.²⁰ It is characterized by a normal early childhood development before the onset of epilepsy and the lack of organic cerebral abnormalities. The main seizure types (myoclonic, myoclonic-astatic, or astatic seizures) start in the first five years of life. In the EEG a presence of generalized 2 to 3 Hz spike- or polyspike-wave complexes without focal spike discharges is seen. In the differential diagnosis severe and benign myoclonic epilepsy in infancy and early childhood, additionally cryptogenic LGS as well as atypical benign partial epilepsy/pseudo LGS, and other symptomatic/cryptogenic epilepsies such as frontal lobe epilepsy must be excluded.²¹ The course of myoclonic-astatic epilepsy in general is unpredictable. In some patients it is self-limited and the seizures disappear. Other children have a more severe course with prolonged episodes of nonconvulsive status epilepticus leading to cognitive and behavioral impairment and mental retardation in parts turning into a LGS.²² Treatment of myoclonic-astatic epilepsy often remains challenging with valproic acid as first line drug.²³ Add-on therapy with lamotrigine which has shown efficacy especially in myoclonic and myoclonic-astatic seizures is another option, but the slow titration of lamotrigine limits its use in patients with lots of seizures or nonconvulsive status epilepticus. Ethosuximide is recommended especially

in absences and myoclonic seizures. The use of small doses of benzodiazepines, levetiracetam, and topiramate are other alternatives.²¹ Oguni and colleagues²³ recommended as most effective treatment for myoclonic astatic seizures the ketogenic diet, followed by adrenocorticotrophic hormone (ACTH) and ethosuximide. Especially in the beginning of myoclonic-astatic epilepsy the differential diagnosis of LGS may be very difficult. This has been reflected in the past by summarizing both these epilepsy forms under the rubric of “myoclonic epilepsies”.²⁴

For myoclonic-astatic epilepsy, four patients were reported in more heterogeneous series (three by Kluger et al¹³ and one by Coppola et al⁷), and a further eight refractory patients with myoclonic-astatic epilepsy by Stupnagel et al.⁹ The first four patients were all responders with a 50% to 99% improvement in seizure frequency after a follow-up of 12 to 36 months.

After a follow-up of 18 months, all three patients by Kluger et al¹⁹ were still taking rufinamide and 1 of them showed a >50% seizure reduction. More recently, Von Stupnagel et al⁹ evaluated the effectiveness and tolerability of rufinamide in eight children with pharmacoresistant myoclonic-astatic epilepsy in a retrospective European multicentric study. Overall, the responder rate after 3 months (reduction of seizure frequency $\geq 50\%$ in comparison with 4 weeks before starting therapy with rufinamide) was 87.5%. Six of the initial responders showed some loss of efficacy after 6 months (decrease in the reduction of seizure frequency from initially 75% to 50%, one patient no longer showed a therapeutic effect), while responder rate after 18 months was 33%. The authors concluded that in this small group of patients with myoclonic-astatic epilepsy, rufinamide may be effective especially for drop-attacks but with a loss of long-term efficacy.

Dravet syndrome (severe myoclonic epilepsy of infancy) is characterized by prolonged febrile seizures starting at about the age of 6 months. Other types of seizures might be present at onset or develop later including myoclonic seizures, complex partial seizures, generalized tonic-clonic seizures and, sometimes, alternating hemiclonic seizures. Although psychomotor development is initially normal, a plateau occurs usually in the second year of life with subsequent intellectual disability.²⁵ Mutations in SCN1A coding for the alpha-1 subunit of the voltage-gated sodium channel can be detected in up to 80% of children.^{26–28} Dravet syndrome is a difficult-to-treat epilepsy syndrome. Treatment of Dravet syndrome remains challenging and is based on the use of a maintenance AEDs therapy, prevention of infectious diseases, control of hyperthermia, and intermittent rescue

treatment with benzodiazepines. Randomized controlled studies of AED use in Dravet syndrome have only been published for add-on treatment with stiripentol.²⁹

The first data reported on Dravet syndrome and rufinamide were for six patients, two reported by Kluger et al,¹³ and four by Coppola et al.⁷ One of two patients initially reported by Kluger et al,¹³ with SCN1A mutation and Dravet syndrome, had a 90% reduction in generalized tonic-clonic seizures. This patient was severely handicapped and had been refractory to previous treatment with eleven conventional AEDs. Though still on rufinamide after 18 months, this patient was no longer considered as a responder.¹⁹ One of the four patients with Dravet syndrome reported by Coppola et al⁷ had a 25% to 49% seizure reduction after a mean 11.4 month observational period. Seizure frequency remained unchanged in another one and increased in other two. Recently, Mueller et al¹¹ reported efficacy and tolerability of rufinamide in 20 patients with Dravet syndrome and refractory seizures in a retrospective European multicenter study. Sixteen of 20 patients had a SCN1A mutation. The responder rate was 20% after 6 months, and 5% after 34 months. The retention rate was 45% after 6 months, 15% after 18 months, and 15% after 34 months. Rufinamide treatment was stopped due to seizure aggravation in about one-third of the patients. Therefore, these authors state that rufinamide does not seem to be a suitable option for long-term treatment in patients with Dravet syndrome.

Malignant migrating partial seizures in infancy (MMPSI) is a rare and severe syndrome first reported in 1995 by Coppola et al.³⁰ MMPSI was included among the childhood epilepsy syndromes in the development of the proposal to revise the International League Against Epilepsy (ILAE) classification of epilepsies and epilepsy syndromes¹² and, more recently, placed between the Ohtahara syndrome and West syndrome in the list of electroclinical syndromes and other epilepsies presented by age at onset, as provided by the ILAE Commission on Classification and Terminology.^{20,31}

The main features of the syndrome are seizure onset within the first semester of life in a previously normal child, focal seizures that typically migrate from one area to another in one hemisphere or from one hemisphere to the other, marked drug resistance, and severe long-term outcome.³⁰

Since 1995, more than 60 cases have been reported^{32–36} and, from the first series,³⁰ a few cases with seizure onset in the first day of life³⁴ or with a less unfavorable outcome have been described.^{33,35}

Etiology remains largely unknown. The hypothesis of a genetic component has failed to be proved despite the

genetic testing of a large series for several ion channel genes.³⁷ To date, familial recurrence of this syndrome has not been reported.

Very recently, Vendrame et al¹⁰ reported the retrospective data on the efficacy of rufinamide in five infants (three males) with malignant migrating partial epilepsy of infancy (MMPEI), aged between 25 and 41 months (median 30 months). Age at seizure onset ranged between 15 days and 3.5 months (median 1.5 month). Rufinamide was added to one of two AEDs (levetiracetam, 2; lamotrigine, 1; topiramate, 1; zonisamide, 1) in four children and given alone in another one, at the daily dose of 5 to 75 mg/kg.

Two of the five cases had a dramatic response to rufinamide with a >50% reduction in seizure frequency and no side effects. In another case rufinamide was discontinued because of vomiting, and in the other two cases rufinamide led to seizure worsening (in one patient as monotherapy), and had to be withdrawn within 2 to 4 weeks. Reported side effects were vomiting and loss of appetite, similar to side effects that have been previously described. In conclusion, rufinamide showed good efficacy and tolerability in two of the five cases with MMPEI. Although limited, these observations provide hope for a novel therapeutic option in this otherwise devastating epileptic syndrome.

Rufinamide in partial seizures

Data on rufinamide for the treatment of partial seizures in the pediatric population are currently scarce (no more than 60 patients) and have to be pooled out from a few series.

Kluger et al¹³ in a heterogeneous group of 45 children and 15 adults with refractory epilepsy, reported that the lowest responder rate (23.5%) was found among the 17 patients with partial epilepsy. Data were collected after a 3-month observation period during which patients received a mean final dose of rufinamide of 35.6 ± 17.3 mg/kg/day, generally achieved within 4 weeks. Add-on therapy with rufinamide was usually initiated at 10 mg/kg/day and valproic acid and clobazam were the most commonly used concomitant AEDs.

Indeed, of the four responders, three had a seizure reduction of 50%–75% and 1 of 75%–99%. Accordingly, with respect to disabling seizure types, the lowest responder rates were also observed for partial seizures (26.0%), while the highest for tonic fits and drop-attacks (45% and 47.1%, respectively).

Indeed, three of four responders had a seizure decrease of 50% to 75% and another 1 of 75% to 99%.

It is, however, unknown how many of these patients belong to pediatric age. Accordingly, these authors state that their result is in concordance with previous studies

Table 1 Review of tolerability and adverse events in pediatric patients treated with rufinamide

References	Number of patients	Age range (years) median or mean	Study design	Type of population	Adverse events on RUF no of pts (%) most common AEs (%)	Responder rate (percentage of patients with a total seizure reduction of $\geq 50\%$)
Glauser et al ⁶	138	4–37 (12.0)	Double-blind, randomized, placebo-controlled trial	LGS	41/74 (55.4) somnolence (24.3) and vomiting (21.6)	31.1
Kluger et al ¹³	60	1–50 (14.5 $\pm$ 11.6)	Retrospective observational study	Focal or generalized refractory epilepsy	25/60 (41.7) fatigue (18.3) vomiting (13.3)	46.7
Olson et al ⁸	38	1.5–23 (7.0)	Retrospective analysis RUF as add-on	Epileptic spasms	14/38 (37.0) increased seizure frequency (13.1) loss of appetite (7.8)	53.0
Kluger et al ¹⁹	52	14.9 $\pm$ 12.1	Long-term extension phase study RUF as adjunctive drug	Focal or generalized childhood-onset refractory epilepsy	37/60 (51.7) fatigue (18.3) vomiting (15.0) loss of appetite (10.0)	46.7 > 3 months 26.7 > 18 months
Coppola et al ¹⁵	43	4–34 (15.0)	Prospective, add-on, open label treatment study	LGS	10/43 (23.2) vomiting (13.5) irritability (6.9) drowsiness (2.3) rash (2.3)	60.5
Kluger et al ¹⁴	124	4–37 (14.2)	Long-term, open label, extension phase (432 days)	LGS	87/124 (70.2) vomiting (30.6) pyrexia (25.8) URTI (25.8)	41.0
Coppola et al ⁷	38	3–34 (12.5)	Prospective, add-on open label therapy study	Refractory childhood epileptic encephalopathies	somnolence (21.8) 11/38 (39.5) vomiting (28.9) drowsiness (5.3) irritability (5.3)	39.5
Vendrame et al ¹⁶	77	1–27 (12.0)	Retrospective analysis as add-on drug	Focal or generalized epilepsy	23/77 (29.0) drowsiness (13.0) rash (6.0) anorexia (2.0)	LGS (38.4) WS (14.3) FCS (83.3) FSS (31.3)
Mueller et al ¹¹	20	3–23 (12.2)	Retrospective European multicenter study	Dravet syndrome	8/20 (40.0) fatigue (10.0) gait disorders (5.0)	20.0 > 6 months 5.5 > 34 months
Von Stupnagel et al ⁹	8	3.7–20.2 (7.3)	Retrospective analysis	Doose syndrome	2/8 (25.0) decreased appetite (50.0) sleepiness (12.5)	87.5 > 3 months 33.0 > 18 months
Vendrame et al ¹⁰	5	2.1–3.11 (2.6)	Retrospective analysis	Malignant migrating partial seizures in infancy	3/5 (60.0) vomiting (20.0) loss of appetite (20.0)	40.0

Abbreviations: AEs, adverse events; URTI, upper respiratory tract infections; PLB, placebo; RUF, rufinamide; LGS, Lennox-Gastaut syndrome; WS, West syndrome; FCS, focal cryptogenic seizures; FSS, focal symptomatic seizures.

demonstrating responder rates between 11.0% and 20.4% in adults and adolescents with partial onset seizures.^{4,38}

The same authors¹⁹ in an extension follow-up study of the same series of 60 patients reported the worst outcome after 18 months for the patients with partial seizures (11.8%), of whom only two of 17 were still responders and three of 17 (17.6%) were still taking rufinamide. On the contrary, the retention rate after 18 months of the other generalized epilepsy syndromes including Lennox-Gastaut syndrome was 51.6%.

As to the origin of focal seizures, those starting from frontal lobes, even in patients with multifocal epileptic encephalopathies, were particularly sensitive to rufinamide treatment.⁷ In more detail, in the group with (bi)frontal spike-wave discharges, seven of eleven patients (63.6%), all of them with drop-attacks, had a seizure reduction of $\geq 50\%$; conversely, in the group without frontal discharges, in which focal and tonic seizures were most frequent, seven of 22 patients (31.8%) showed a $\geq 50\%$ seizure decrease.

Last, Vendrame et al,¹⁶ in a retrospective analysis of 77 patients with diverse refractory epilepsy syndromes and receiving rufinamide as adjunctive therapy, reported the highest responder rate in focal cryptogenic epilepsies (83.3% of patients with $\geq 50\%$ of response rate), and in diverse seizure types, with the highest responder rate in tonic/atonic and partial seizures (48.6% and 46.7% of patients with $\geq 50\%$ response rate, respectively). Of note is that the number of patients with cryptogenic focal seizures is small (twelve cases), while a $\geq 50\%$ seizure reduction in symptomatic partial seizures was present in only 31.3% of cases. Further, an early response was evident at doses as low as 10 mg/kg/day, with no further benefits above the recommended dose. Similarly, no correlation was evident between decrease in seizure frequency and number or type of AEDs used together with rufinamide.

Safety and tolerability of rufinamide

A recent, pooled analysis of seven clinical studies by Wheless et al³⁹ comprising 212 rufinamide-treated (age range 3–16 years) and 197 placebo patients (age range 4–17 years) in the double-blind studies, and 391 patients receiving rufinamide in the double-blind and/or open label extensions, the most common adverse effects observed in rufinamide-treated patients in the double-blind studies were somnolence, vomiting, and headache. Changes in laboratory values, vital signs, and weight were generally clinically insignificant. Accordingly, these authors state that rufinamide in pediatric patients, mainly as adjunctive therapy, shows a

favorable safety and tolerability profile. An up-to-date review of adverse events in pediatric patients treated with rufinamide in eleven clinical studies (Table 1) seems to confirm previous data, even extending the favorable tolerability and safety profile of rufinamide to long-term administration.

Conclusion

Data emerging from literature confirm that rufinamide deserves a privileged role in the treatment of LGS, for which it is granted orphan drug status. Efficacy of rufinamide mostly against atonic-tonic seizures in these patients is also undoubted, and explains why this drug is now considered a second-line therapy together with lamotrigine, levetiracetam, topiramate, and zonisamide, to be combined with valproic acid, which still remains the first-line therapy option.⁴⁰

Probably, rufinamide should be preferred to other drugs such as lamotrigine and topiramate when drop-attacks and/or tonic fits are the main seizure type and, of course, before felbamate, other newer anticonvulsant drugs, vagus nerve stimulation, or corpus callosotomy is considered.

Overall, rufinamide may be considered a second-line therapy for LGS to be added to valproic acid, which remains the first-choice drug. Rufinamide should be considered among one or two of the following: lamotrigine, levetiracetam, topiramate, and zonisamide, and should be probably preferred early if atonic-tonic fits occur.

It has in addition the advantage of full therapeutic dosing within 1 week, whereas other approved medications, lamotrigine and topiramate, can take up to 2 months to reach therapeutic values.

Preliminary data also seem to confirm the efficacy of rufinamide in epileptic encephalopathies other than LGS, including myoclonic-astatic epilepsy and Lennox-like multifocal encephalopathies, particularly those with (bi)frontal spike and wave discharges and tonic/atonic seizures. Less encouraging appears to be the efficacy of rufinamide in Dravet syndrome and malignant migrating partial seizures in infancy. Overall, rufinamide appears to be less effective against focal-onset seizures compared with generalized encephalopathies, though this issue is still controversial and further studies are warranted especially in pediatric patients.

Titration schedule should be as slow as possible, though a short escalation period with increasing dose at each 3-day interval is usually recommended in the packet insert. A slow titration phase improves tolerability, allowing assessment of clinical efficacy at low doses in some patients and detection of seizure worsening in others.

As regards the daily dose, an early response may be evident at a dose as low as 10 mg/kg/day or even less. A mean maintenance dose of 35 ± 20 mg/kg/day seems most used, though the optimal dose should be tailored according to clinical response.

So far, little is known about therapeutic blood levels, though the mean plasma rufinamide concentration to reduce seizure frequency by 25% to 50% is predicted to be 15 to 30 $\mu\text{g/mL}$.³

Overall, rufinamide is a well-tolerated anticonvulsant drug, and most expected adverse side effects are vomiting, drowsiness, irritability, and loss of appetite. They are usually mild and transient.

For now, rufinamide is a welcome addition to the treatment armamentarium for refractory childhood epilepsy and further studies are needed to better shape its clinical efficacy in children with epilepsy.

Disclosure

The author declares no conflicts of interest.

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