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Rufinamide in children and adults with Lennox–Gastaut syndrome: First Italian multicenter experience

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ABSTRACT

This is the first multicenter Italian experience with rufinamide as an adjunctive drug in children, adolescents and adults with Lennox–Gastaut syndrome.

The patients were enrolled in a prospective, add-on, open-label treatment study from 11 Italian centers for children and adolescent epilepsy care. Forty-three patients (26 males, 17 females), aged between 4 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 were diagnosed as cryptogenic and 23 as symptomatic. Rufinamide was added to the baseline therapy at the starting dose of 10 mg/kg body weight, evenly divided in two daily doses and then increased by 10 mg/kg approximately every 3 days up to a maximum of 1000 mg/day in children aged ≥4 years with a body weight less than 30 kg. In patients more than 30 kg body weight, rufinamide could be titrated up to 3200 mg/day.

After a mean follow-up period of 12.3 months (range 3–21 months), the final mean dose of rufinamide was 33.5 mg/kg/24 h (range 11.5–60) if combined to valproic acid, and of 54.5 mg/kg/24 h (range 21.8–85.6) without valproic acid. The response rate (≥50% decrease in countable seizures) was 60.5% (26 of 45 patients) in total; 51.1% experienced a 50–99% reduction in seizure frequency and complete seizure control was achieved in the last 4 weeks follow-up by 9.3% of patients. Two patients (4.7%) had a 25–50% seizure reduction, while seizure frequency remained unchanged in 13 (30.2%) and increased in 2 (4.7%). Reliable data for atypical absence seizures and myoclonic seizures were not available, as these are usually impossible to count.

Ten patients (23.2%) reported adverse side effects, while taking rufinamide. They were generally mild and transient and most frequently included vomiting, drowsiness, irritability and loss of appetite.

In conclusion, rufinamide as an adjunctive therapy reduced the number of drop attacks and major motor seizures in about 60% of patients with Lennox–Gastaut syndrome and produced only mild or moderate adverse side effects.

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1. Introduction

Rufinamide is a structurally triazole-derivative (1-[2,6-difluorophenyl)methyl]-1hydro-1,2,3-triazole-carboxamide) novel antiepileptic drug, structurally unrelated to the existing antiepileptic drugs, and marketed in Italy since the beginning of 2009. The

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proposed mechanism of action is the limitation of excessive sodium-dependent action potential firing.[1,2] Rufinamide has a broad efficacy spectrum in rodent seizure models of epilepsy.[3] In three RCT trials rufinamide was effective and safe for the adjunctive treatment of partial seizures in adults and adolescents,[4,5] as well as for the treatment of generalized seizures associated with Lennox–Gastaut syndrome (LGS).[6]

A 3-year open-label follow-up study reports continued rufinamide effectiveness as adjunctive therapy in patients with Lennox–Gastaut syndrome.[7]

Furthermore, a recently published multicenter study from Europe using observational retrospective data, confirmed rufinamide to be effective in children and adults with refractory epilepsy, including Lennox–Gastaut syndrome.[8]

Rufinamide was granted orphan drug status in the adjunctive treatment of Lennox–Gastaut syndrome by the European Medicines Agency (EMEA) and the U.S. Food and Drug Administration (FDA) in 2004. Additionally, a marketing authorization approval for use of rufinamide as adjunctive therapy of seizures associated with LGS syndrome in children 4 years and older was granted by the EMEA in 2007, and by FDA in 2008.

Nonetheless, the number of patients treated with this medication is still limited, and a larger number of studies are needed to better establish the role of rufinamide in the overall treatment algorithm for this syndrome.[9]

The purpose of this paper is to report on the first multicenter Italian experience with rufinamide as add-on drug in children, adolescents and adults with Lennox–Gastaut syndrome and difficult-to control seizures.

2. Materials and methods

Patients were recruited in a prospective, add-on, open-label treatment study from 11 Italian centers for pediatric and adolescent epilepsy care. The patients were selected according to the following criteria: (1) age 4 years and over; (2) Lennox–Gastaut syndrome refractory to at least three previous antiepileptic drugs (AEDs), alone or in combination; (3) more than one seizure per month in the last 6 months; (4) use of at least one other AED, but no more than three, at baseline; (5) informed consent from parents and/or caregivers, who had to be able administer the study drug and record seizures in a diary. Moreover, female patients of child bearing age were required not to be pregnant and to be using an adequate form of contraception.

Exclusion criteria included progressive neurological or systemic disease. Patients with significantly abnormal liver, kidney and blood laboratory values were also excluded, as were those who were considered unlikely to comply with the study requirements.

Besides enrolling rufinamide-naïve subjects, study sites that had previously started patients on rufinamide had the option of enrolling patients who had completed at least 6 months of maintenance treatment and met the study inclusion and exclusion criteria. This means that some patients could be retrospectively included.

Pseudo-seizures were excluded by means of video-EEG recordings and/or long-term monitoring EEGs. CT and MRI were performed in all cases. The number of the seizures was recorded by parents and/or caregivers at home and at school. Seizure frequency, type and duration were recorded in an epilepsy diary reviewed at each follow-up visit. All seizures were classified according to the International League against Epilepsy Revised Classification of Seizures (ILAE Commission, 1981),[10] while diagnostic criteria for Lennox–Gastaut syndrome were based on the International League Against Epilepsy classification (1989) as follows: (1) polymorphous seizures including tonic–axial, atonic, and absence seizures (other types such as myoclonic, GTCS, or partial seizures are frequently associated); (2) EEG abnormal background activity, slow spike-waves <3 Hz and, often multifocal abnormalities, and bursts of 10 Hz fast rhythms during sleep; (3) in general, mental retardation.[11] There was an initial observation period of 6 months (baseline) that could be shortened to 3 months if seizures occurred almost daily. After the observation period, rufinamide was added to the baseline therapy at the starting dose of 10 mg/kg body weight, evenly divided in two daily doses and then titrated by 10 mg/kg per day approximately every 3 days up to a maximum of 1000 mg/day in children aged $\geq$4 years with a body weight less than 30 kg. If baseline therapy included valproic acid, rufinamide could be titrated up to a maximum of 600 mg/day, because of the significantly reduced clearance, especially in children, of rufinamide in combination with valproic acid. In patients more than 30 kg body weight, rufinamide could be titrated up to 1800 mg/day if body weight was comprised between 30.0 and 50.0 kg, up to 2400 mg/day for body weight of 50.1 to 70.0 kg, and up to 3200 mg for body weight of more than 70.1 kg.

During titration and maintenance periods, anticonvulsant drug daily doses including rufinamide could be changed whenever necessary depending on clinical and adverse side effects. Rescue drugs were allowed if necessary. EEG, adverse effects and blood levels of concomitant anticonvulsant drugs were monitored in all patients. Patients were followed on a weekly basis during the titration period, either by means of visits to the clinic or by telephone. Patients subsequently visited the clinic at 3-month intervals during the maintenance treatment, with a monthly follow-up by telephone between visits to the clinic whenever necessary. Blood chemistry and liver and kidney function were carefully assessed at each time interval. Parents/caregivers were informed of the potential clinical adverse effects and to refer any such side effects to the clinician.

Efficacy was assessed by comparing the frequency of countable seizures at baseline (4 weeks before rufinamide therapy) with the frequency in the last 4 weeks of observation.

The response to treatment was monitored in terms of reduction of seizure frequency, in relation to the baseline phase, using the following categories: (1) seizure control (100% seizure remission); (2) 50–99% decrease in number of seizures; (3) 25–49% decrease in number of seizures; and (4) worsened when the seizure rate and/or severity increased by $\geq$25% as compared to baseline period.

The Institutional Review Board from each epilepsy unit approved the study; no support was received from pharmaceutical companies.

Statistical evaluation was performed by means of a two-tailed Wilcoxon Rank test for non-parametric data and the Fisher exact test. Data were expressed as mean $\pm$ SD and median values. Significance was set at $p < 0.05$.

3. Results

Forty-three patients (26 males, 17 females), aged between 4 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 were diagnosed as cryptogenic, and 23 as symptomatic Lennox–Gastaut syndrome (9 brain atrophy, 9 migration disorder, 4 brain malformation, 1 tuberous sclerosis). Mental retardation (MR), evaluated before starting rufinamide by Brunet–Lezine[12] or Terman–Merrill[13] tests, was present in all patients: mild MR was detected in 12 patients, moderate in 6, severe in 15, and profound in 10. Neurological examination at the time of entry revealed abnormalities in 35/43 patients (81.4%) with minor motor impairments in 16, hemiparesis in 2, spastic tetraplegia in 11, diplegia in 1, ataxia in 3, generalized hypotonia in 2. CT/MRI scans showed abnormal finding in 23/43 patients (53.5%): brain atrophy (9),

Table 1
Seizure outcome following treatment with adjunctive rufinamide in different age groups.

Age (years)	Number initiating (*n*)	Seizure control	At follow-up (mean follow-up 12.3 months)	Seizure etiology	Adverse side effects	Mean number AED	Type of treatment
4–7	4	Seizure free	–		–	C (2.5)	
		50–90%	4 (100%)	C (4)			(VPA-CNZ); (VPA-PB-CNZ); (VPA-LTG-CNZ); (ZNS-OXC)
		25–50%	–				
		Unchanged	–				
		Increased	–				
8–12	11	Seizure free	1 (9.1%)	C (1)	3 (27.3%)	C (2.3)	(VPA-LEV)
		50–90%	7 (63.6%)	C (1) S (6)		S (2.2)	3 (VPA-LEV); (VPA-LEV-CNZ); (VPA-LEV-ETS); (LTG-CLOB); (VPA-ETS)
		25–50%	1 (9.1%)	C (1)			(VPA-FBM-CLOB)
		Unchanged	2 (18.2%)	S (2)			(VPA-CNZ); (VPA-TPM)
		Increased	–				
13–18	20	Seizure free	3 (15%)	C (3)	5 (25%)	C (2.5)	(VPA-LEV-CNZ); (VPA-LTG-CNZ); (PB-FBM-OXC)
		50–90%	8 (40%)	C (3) S (5)		S (2.2)	(FBM-OXC); (VPA-FBM); (VPA-LEV-TPM); (VPA-LTG); (VPA-ETS); (CBZ-PB); (LEV-CLOB); (VPA-LEV-CLOB)
		25–50%	1 (5%)	C (1)			(LEV)
		Unchanged	7 (35%)	C (4) S (3)			(VPA-CBZ-CLOB); (OXC-PB-LEV); (OXC-LTG); (VPA-FBM-CNZ); (LTG-TPM); (VPA-FMB); (VPA-PHT)
		Increased	1 (5%)	S (1)			(VPA-ZNS-FBM)
>18	8	Seizure free	–		2 (25%)	C (3)	
		50–90%	3 (37.5%)	C (1) S (2)		S (3)	2 (VPA-LEV-ZNS); (LTG-TPM-CBZ)
		25–50%	–				
		Unchanged	4 (50%)	C (1) S (3)			(LEV-PB-LTG); (VPA-LEV-TPM); (LEV-TPM-PB); (VPA-LTG-TPM)
		Increased	1 (12.5%)	S (1)			(VPA-CBZ-CNZ)

C, cryptogenic; S, symptomatic; AED, antiepileptic drug; VPA, valproic acid; PB, phenobarbital; CNZ, clonazepam; LTG, lamotrigine; ZNS, zonisamide; OXC, oxcarbazepine; CBZ, carbamazepine; LEV, levetiracetam; FBM, felbamate; CLOB, clobazam; TPM, topiramate; PHT, phenitoine.

disorders of neuronal migration (9), brain malformations (4), tuberous sclerosis (1). Seizure types, generally associated in a given patient before the introduction of rufinamide, were classified as follows: atypical absences in 14 (32.5%), drop-attacks (atonic and/or myoclonic) in 35 (81.4%), tonic in 22 (51.2%), tonic–clonic in 12 (27.9%), and complex partial seizures in 6 (20.9%). Seizure frequency during baseline phase was the following: < -1/day (10); 1–20/day (33).

Mean age at seizure onset was 2.2 ± 2.1 years (median 1.0). Mean duration of epilepsy was 13.8 ± 7.9 years (median 12.0). The mean number of anticonvulsant drugs tried before rufinamide was 7.8 ± 2.0 (median 7.5). A final mean dose of rufinamide was 33.5 mg/kg/24 h (range 11.5–60 mg/kg/24 h) if combined to valproic acid, and of 54.5 mg/kg/24 h (range 21.8–85.6 mg/kg/24 h) without valproic acid. All patients received concomitant antiepileptic therapy. Valproic acid (69.8%), levetiracetam (39.5%), clonazepam (20.9%), and lamotrigine (20.9%) were the most commonly used concomitant antiepileptic drugs (Table 1).

3.1. Efficacy

The results are summarized in Table 1. Nine of 43 patients (20.9%) had an observational period of 3 months; seven of them discontinued treatment within 1–5 months because of inefficacy (4) or adverse events (3).

Twenty-six of 43 patients (60.5%) receiving rufinamide as adjunctive therapy had a $\geq$50% seizure reduction in countable seizures after a mean 12-month observational period (Table 1). Complete seizure freedom was achieved in four patients (9.3%). Two patients had a 25–50% seizure reduction, while seizure frequency remained unchanged in 13 (30.2%) and increased in two patients (4.7%).

Regarding the seizure type, 20 of the twenty-six responders (78.9%) had a $\geq$50% reduction in drop attacks (six patients were seizure free), and 15 of 26 responders (57.7%) had a $\geq$50% decrease in tonic seizures (four patients were seizure free).

Tonic–clonic seizures improved by 50% or more in 5/26 responders (11.6%).

Reliable data for atypical absence seizures and myoclonic seizures were not available, as these are usually impossible to count.

There was no statistical difference between the characteristics of the responders and non-responders with respect to age at seizure onset, epilepsy duration and age at rufinamide exposure ($p > 0.05$ at Wilcoxon Rank Sum test).

Table 2 shows that there is not a significant difference as to a $\geq$50% seizure reduction between cryptogenic group and symptomatic group (65% vs 56.5%, respectively; $p \geq 0.05$). Nonetheless, drop-attacks were to some extent better controlled in the cryptogenic group (60% vs 34.7%; $p = 0.23$).

Table 2
Efficacy of rufinamide in patients with cryptogenic or symptomatic Lennox–Gastaut syndrome.

	Cryptogenic No. of patients (20)	Symptomatic No. of patients (23)
Seizure control		
100%	4 (20%)	–
50–99%	9 (45%)	13 (56.5%)
25–49%	2 (10%)	–
Unchanged	5 (25%)	8 (34.8%)
Increased	0 (0%)	2 (8.7%)
Drop-attacks		
100%	4 (20%)*	2 (8.7%)*
50–99%	8 (40%)*	6 (26%)*
Tonic seizure		
100%	4 (20%)°	–
50–99%	4 (20%)°	7 (30.4%)°
Tonic–clonic seizure		
100%	2 (10%)	–
50–99%	2 (10%)	1 (4.3%)

* $p = 0.23$ at Fisher exact test.
° $p = 0.43$ at Fisher exact test.

Table 3
Adverse events in LGS patients treated with rufinamide as add-on therapy.

Adverse events[a]	No. of patients (10/43) (23.2%)
Vomiting and /or gastrointestinal disorders	6 (13.5%)
Irritability/aggressiveness	3 (6.9%)
Drowsiness	1 (2.3%)
Skin rash	1 (2.3%)
Decreased appetite	1 (2.3%)

[a] Associated in some patients.

3.2. Safety and tolerability

Ten patients (23.2%) reported adverse side effects, while taking rufinamide (Table 3). Vomiting was present in six patients, leading to drug discontinuation in three patients after 1, 3 and 5 months, respectively. In these patients seizures were unchanged in two and increased in one; noteworthy, all three patients were taking baseline felbamate and valproic acid. In two more patients, vomiting and/or gastrointestinal disorders were transient, while in another one vomiting appeared at rufinamide daily dosage of 53.3 mg/kg. In this patient, vomiting promptly disappeared, when the daily dose was decreased by half. In these patients with vomiting or nausea the mean dose of rufinamide was 34.4 mg/kg/day (11.5–56.2 mg), and the mean blood level of valproic acid was 61.5 mg/L (56–78 mg). Drowsiness, decreased appetite, skin rash and irritability manifested in other five patients; they were transient and mild in all cases.

Seizure worsening was reported in 2 of 43 patients (4.6%), both coming from the symptomatic group, within 1 month after starting rufinamide. Blood levels of concomitant anticonvulsant drugs were generally not modified by the addition of rufinamide. All the patients' laboratory test values were normal.

4. Discussion

In this prospective, open-label add-on study, rufinamide significantly reduced the overall seizure frequency in approximately 60% of patients with Lennox–Gastaut syndrome who had been resistant to at least three previous antiepileptic drugs. This is, to our knowledge, the first multicenter Italian trial with this drug. In addition, drop attacks, tonic seizures and, to a lesser extent, tonic–clonic seizures best responded to this therapy. With respect to seizure etiology, there was a trend to a better response to rufinamide for drop-attacks in cryptogenic cases, although it was not statistically significant ($p = 0.23$, at Fisher's exact test). Because of their sudden nature and tendency to produce injury, major seizures (tonic/atonic and tonic–clonic seizures) are easily identifiable by parents or caretakers and represented the main end-point in the present trial in such a catastrophic syndrome.

The overall response to rufinamide observed in this study is consistent with that reported in two previous studies conducted in the US and Europe on children and young adults with Lennox–Gastaut syndrome.[6,8] In the first randomized double-blind, placebo-controlled trial by Glauser et al.,[6] 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%, $p = 0.0015$). Rufinamide also decreased tonic–atonic seizure frequency by 42.5% vs 1.4% on placebo.

The other study by Kluger et al.[8] was an observational trial conducted as a collection of retrospective data regarding children and adults with refractory epilepsy from multiple centres in Germany and Austria. The response rate in a subset of 31 patients with LGS was 54.8%; further, 4 of these 31 patients became seizure free during the study period. Although relative to a study population including refractory epilepsy syndromes other than Lennox–Gastaut patients, the highest responder rates were observed for tonic seizures (45%) and drop attacks (47.1%).

Although a new drug therapy may easily lead to transient improvement in LGS patients, a mean follow-up period of 12.3 months, even if not prolonged, appears quite long to show a persisting efficacy of adjunctive rufinamide in our responders.

Seemingly, data yielded by Kluger et al.[7] on 124 LGS patients receiving rufinamide in an open-label extension at a median dose of 1800 mg/day for a mean duration of 432 days, showed that, 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. Accordingly, Kluger et al.[14] reported in another series that 51.6% of patients with Lennox–Gastaut syndrome were still taking rufinamide after 18 months of follow-up, with a responder rate of about 35.5%.

Worthy of note is the dose-range of rufinamide's maximal efficacy, which in our series was essentially comparable to that reported by Kluger et al.[8]

In agreement with pharmacokinetic studies,[15] blood levels of concomitant antiepileptic drugs were not significantly modified in our patients, thus suggesting that rufinamide's effects were not substantially influenced by concomitantly administered therapy.

It is noteworthy that seizure worsening on rufinamide was not reported in either patients with LGS[6,8] or partial seizures.[5] In three patients reported by Glauser et al.,[6] status epilepticus appeared 13, 20 and 25 days after starting rufinamide therapy, respectively, leading to drug withdrawal in two patients. In our series, the two patients out of 43 (4.8%) who had seizure increase, showed the following clinical features: one 24-year-old male with bilateral pachygyria developed early seizure worsening whenever a new antiepileptic drug was added to his baseline drug regimen; a second one showed seizure increase on rufinamide when felbamate daily dose was reduced.

So far, seizure worsening on rufinamide is not clearly proven, although such a possibility cannot be ruled out, and further experience with this drug needs to be done.

As shown in Table 1, no clear relationship emerged between the clinical response to rufinamide and any seizure etiology or baseline AED treatment in the different age groups.

Six patients with cryptogenic LGS underwent implantation of a vagus nerve stimulator (VNS) (5) or callosotomy (1), with no significant results on seizure frequency prior to receiving rufinamide. Two of these patients, both on VNS, showed a $\geq$50% reduction in drop attacks on rufinamide after a follow-up period of 4 and 9 months, respectively.

With respect to tolerability, our series disclosed adverse side effects probably linked to rufinamide adjunctive treatment in about 20% of patients, much in keeping with what reported by Glauser et al.[6] and Kluger et al.[8] They frequently appeared early after starting drug titration, and most commonly included vomiting, drowsiness and loss of appetite. In our experience, persistent vomiting led to drug discontinuation in three patients, similarly to what happened in four patients of Kluger et al.[8] and in six patients of Glauser et al.[6] Interestingly, all patients were taking valproic acid together with rufinamide, suggesting a potential risk of this association to expose to such an adverse event. Unfortunately, the number of patients is too small to draw any conclusion.

Worthy of note is that serious adverse effects have not been reported so far.

In conclusion, in our experience rufinamide reduced seizure frequency in children and young adults with Lennox–Gastaut syndrome, and it was particularly effective against drop-attacks and tonic seizures. Reliable data for atypical absence seizures and myoclonic seizures were not available, as these are usually impossible to count.

Moreover, this drug was generally well tolerated in this study population. This trial seems to confirm what emerged in a few previous studies, although further experience is warranted to gain better understanding of the efficacy of rufinamide both in the long term and in the treatment of well-defined epileptic encephalopathies other than Lennox–Gastaut syndrome.

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