

Rufinamide from clinical trials to clinical practice in the United States and Europe

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ABSTRACT – Rufinamide is a triazole derivative structurally unrelated to other antiepileptic drugs that is indicated for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients aged ≥ 4 years. Originally granted orphan drug status, marketing authorisation was obtained on the basis of a randomised, double-blind, placebo-controlled trial conducted in 138 LGS patients. An open-label extension study subsequently demonstrated that rufinamide's efficacy and tolerability were maintained over the longer term (median duration of treatment, 432 days). Recently published reports from Europe and the United States have described the use of adjunctive rufinamide to treat LGS in clinical practice. These data complement the clinical trial results, by providing information on the efficacy and tolerability of rufinamide when used on an individualised basis in real-world practice, under less tightly restricted conditions in terms of patient population and dosing strategies. A comparison of the data reveals that a "lower and slower" dosing strategy tends to be adopted in clinical practice, in comparison with the clinical trial, which does not appear to compromise efficacy, but may provide improvements in tolerability. Individual case reports provide additional valuable information on how rufinamide is being used to treat different seizure types associated with LGS. Since clinical experience with rufinamide is currently at an early stage, there are still unanswered questions relating to its use, and it is likely that its place in the adjunctive treatment of LGS will evolve as further data emerge.

Key words: clinical practice, clinical trials, Lennox-Gastaut syndrome, real-world, rufinamide

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Rufinamide is a triazole derivative that is structurally unrelated to other antiepileptic drugs (AEDs) (Jain, 2000). Its principal mode of action is thought to be via limiting the firing of sodium-dependent action potentials, although additional mechanisms are likely to be involved, given the broad range of seizure types against which rufinamide is effective (Hakimian *et al.*, 2007). Rufinamide was granted orphan drug status in 2004 for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients aged ≥ 4 years. It was authorised for this indication in Europe in January 2007, and in the United States in November 2008.

Marketing authorisation was obtained on the basis of a multicentre, randomised, double-blind, placebo-controlled, parallel-group trial, which assessed the efficacy and tolerability of adjunctive rufinamide therapy in LGS patients ($n=138$), aged 4-30 years (Glaser *et al.*, 2008). Following 12 weeks' double-blind treatment, patients receiving rufinamide experienced a significant reduction in drop attacks (tonic-atonic seizures) compared with those who received placebo (42.5% vs -1.4%; $p<0.0001$), as well as a significant reduction in total seizures (32.7% vs 11.7%; $p=0.0015$) (Glaser *et al.*, 2008). In addition, a significantly higher proportion of patients treated with rufinamide reported an improvement in seizure severity compared with placebo (53.4% vs 30.6%; $p=0.0041$), and the responder rate – defined as the percentage of patients achieving $\geq 50\%$ reduction in seizures – was significantly higher for patients receiving rufinamide vs. placebo for both drop attacks (42.5% vs 16.7%; $p=0.002$) and total seizures (31.1% vs 10.9%; $p=0.0045$). In general, rufinamide was well tolerated, with the most common adverse events (AEs), reported by $\geq 10\%$ patients and with a higher incidence than placebo, being somnolence and vomiting (Glaser *et al.*, 2008). In a long-term, open-label extension to this study, all patients ($n=124$) received treatment with rufinamide for a median of 432 days (range 10-1149 days) (Kluger *et al.*, 2010a). Reductions in seizure frequency were observed throughout the study; during the last 12 months of treatment, 47.9% of patients achieved a $\geq 50\%$ reduction in drop attacks, with 6.8% of patients becoming free from drop attacks, and 41.0% of patients achieved a $\geq 50\%$ reduction in total seizures. Tolerability observed in the 12-week pivotal trial was maintained over the long term (Kluger *et al.*, 2010a). European regulators requested that further safety data be collected following approval of rufinamide and this information is currently being obtained by means of an ongoing LGS patient registry in Europe (Seeruthun *et al.*, 2009). This paper will discuss how rufinamide is being used in clinical practice, by presenting efficacy and tolerability data from Europe and the United States and comparing its use against data from the pivo-

tal clinical trial and its extension. The paper will also review how rufinamide fits into current treatment guidelines and present case reports illustrating its use in different seizure types associated with LGS.

European experience of using rufinamide to treat LGS

In Europe, it is recommended that, for LGS patients ≥ 4 years of age weighing <30 kg, treatment with rufinamide should be initiated at 200 mg/day and increased by 200 mg/day increments as frequently as every 2 days, to a maximum recommended dose of 1,000 mg/day in patients not receiving valproate and 600 mg/day in those receiving valproate (since valproate significantly decreases rufinamide clearance [Marchand *et al.*, 2010]) (Inovelon[®] SmPC). In patients ≥ 4 years of age weighing ≥ 30 kg, it is recommended that treatment should be initiated at 400 mg/day and increased by 400 mg/day increments as frequently as every 2 days to a maximum recommended dose of 1,800-3,200 mg/day, depending on body weight (Inovelon[®] SmPC).

Recently, results were published of a retrospective observational study conducted in eight sites across Germany and Austria, in which the clinical course of LGS patients treated with rufinamide was documented (Kluger *et al.*, 2009; Kluger *et al.*, 2010b). Efficacy was evaluated by comparing the frequency of seizures during the last 4 weeks of treatment with baseline (4 weeks before rufinamide therapy). The study population included 31 patients with LGS, with a median age of 9.4 years (range 1.9-50.2 years) (Kluger *et al.*, personal communication). Rufinamide was usually initiated at 10 mg/kg/day and a mean \pm SD maintenance dose of 34.4 ± 20.1 mg/kg/day (range 10.0-85.7 mg/kg/day) was generally achieved within 4 weeks (Kluger *et al.*, personal communication). All patients received concomitant AEDs during the 12-week observation period. Overall, 17/31 (54.8%) LGS patients were responders ($\geq 50\%$ seizure frequency reduction), 8 (25.8%) achieving 50-75% seizure frequency reduction, 5 (16.1%) achieving a 75-99% seizure frequency reduction, and 4 (12.9%) achieving seizure freedom during the last 4 weeks of the observation period (*figure 1*) (Kluger *et al.*, 2009). AEs were reported by 16/31 (51.6%) patients with LGS (Kluger *et al.*, personal communication). Most were mild to moderate in intensity and no serious AEs were reported (Kluger *et al.*, personal communication).

In a long-term follow-up to the initial study, all 31 LGS patients continued treatment with rufinamide for up to 18 months (Kluger *et al.*, 2010b). The median rufinamide maintenance dosage was 34.0 mg/kg/day (range 16.0-83.0 mg/kg/day) in patients with LGS (Kluger

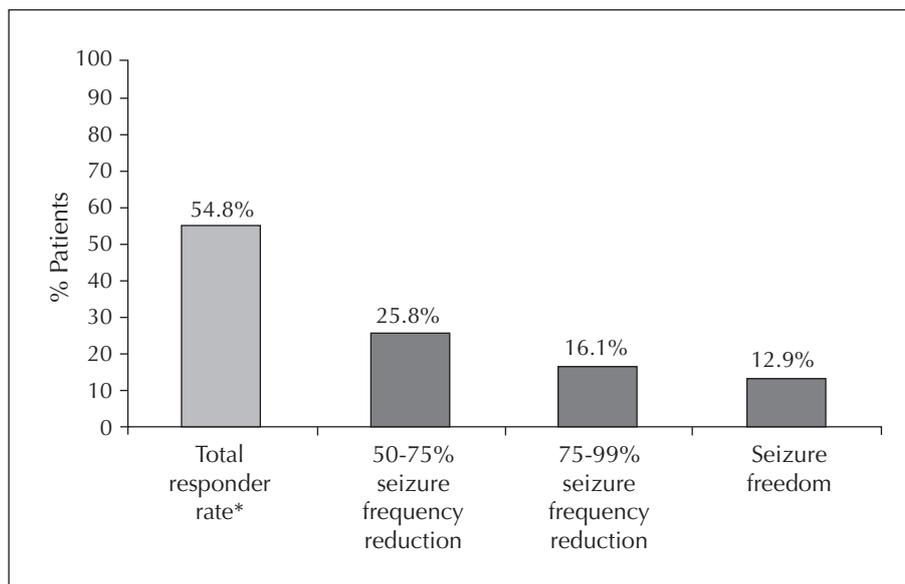


Figure 1. Efficacy of 12 weeks' adjunctive rufinamide therapy in 31 LGS patients treated in eight tertiary epilepsy centres across Germany and Austria (Kluger *et al.*, 2009).

* Response defined as $\geq 50\%$ seizure frequency reduction; data represent seizure frequency reduction observed during the last 4 weeks of a 12-week observation period, compared with the 4 weeks prior to initiation of rufinamide therapy.

et al., personal communication). The retention rate for LGS patients was 51.6% (16/31) (Kluger *et al.*, 2010b). Overall, 11/31 (35.5%) LGS patients were responders, as assessed during the last 4 weeks of the observation period (Kluger *et al.*, 2010b). The safety and tolerability of rufinamide remained favourable throughout the long-term study (Kluger *et al.*, 2010b).

Results of a long-term, prospective, add-on, open-label study conducted in LGS patients recruited from 11 centres in Italy have also recently been published (Coppola *et al.*, 2010). Rufinamide was added to baseline therapy at a starting dose of 10 mg/kg/day and uptitrated approximately every 3 days in accordance with labelling recommendations (Inovelon[®] SmPC). Efficacy was assessed as per the German/Austrian study. The study population comprised 43 patients with either cryptogenic (n=20) or symptomatic (n=23) LGS. The final mean rufinamide dose was 33.5 mg/kg/day (range 11.5-60.0 mg/kg/day) if combined with valproate and 54.5 mg/kg/day (range 21.8-85.6 mg/kg/day) without valproate, and all patients received concomitant AEDs (Coppola *et al.*, 2010). After a mean follow-up period of 12.3 months (range 3-21 months), 26/43 patients (60.5%) were responders, with 4/43 (9.3%) achieving complete seizure freedom; 2/43 (4.7%) experienced 25-50% seizure frequency reduction; 13/43 (30.2%) experienced no change in seizure frequency; and 2/43 (4.7%) experienced an increase in seizure frequency (Coppola *et al.*, 2010). Ten patients (23.2%) reported AEs while taking rufinamide. Vomiting led to rufinamide discontinuation in three patients; other AEs were transient and mild (Coppola *et al.*, 2010).

Several other open studies conducted in Europe have assessed the efficacy and tolerability of rufinamide treatment in LGS patients in clinical practice (table 1). Since LGS is a rare type of epileptic encephalopathy, rufinamide was licensed on the basis of a single randomised controlled trial, conducted in 138 patients (74 patients randomised to receive rufinamide) (Glauser *et al.*, 2008), with the European Medicines Agency requesting that a post-marketing patient registry be set up in order to additionally assess the long-term safety of the drug. In response to this, a European registry was established to provide long-term data (≥ 3 years) on at least 100 LGS patients initiating rufinamide as add-on therapy and up to 300 LGS patients receiving other AEDs (Seeruthun *et al.*, 2009). The primary objective of the registry is to evaluate safety during the use of rufinamide and other AEDs in combination therapy to treat LGS, but it will also allow assessment of other aspects of LGS management, such as healthcare resource utilisation (Seeruthun *et al.*, 2009). The registry includes patients aged ≥ 4 years who require modification to their current AED medication, including (but not limited to) initiation of add-on rufinamide therapy (Seeruthun *et al.*, 2009).

US experience of using rufinamide to treat LGS

In the United States, for children with LGS aged ≥ 4 years, treatment with rufinamide should be initiated at approximately 10 mg/kg/day in two equally

Table 1. Summary of additional studies conducted in Europe in which rufinamide has been used in clinical practice.

Authors	Setting	Population	Rufinamide dosing	Previous/ concomitant treatment	Follow-up	Efficacy	Tolerability
Friedo <i>et al.</i> , 2009	CP Germany	Adults with phar- macoresistant epilepsies (n = 22); 16M/6F; mean age 32.5 years (range 19-48 years). 16 patients with LGS	Slow titration: +200 mg/3-7 days; target 1200-3200 mg/day	Concomitant AEDs used: 1, n = 2; 2-4, n = 20 (mean 2.3)	Mean 5.3 months (range 2-8 months)	Assessed in 16 patients. 9/16 achieved > 50% seizure frequency reduction; 3/16 patients achieved > 75% seizure frequency reduction. No seizure freedom or worsening of seizures observed	6/22 patients had RUF-associated AEs: toxic cerebellar syndrome, sleepiness
Wiemer- Kruel <i>et al.</i> , 2009	CP (single centre) Germany	Children with LGS (n = 11); 6M/5F; age 5-17.5 years	Slow titration up to 40 mg/kg/day. Recommend titrating in 100-200 mg increments every 5-7 days from 10 to 40 mg/kg/day, to avoid AEs	High previous use of AEDs (up to 24). VNS in 2 patients	Only given for 2 patients: 5 and 8 months. (5 patients currently being titrated)	Positive response (seizure reduction) only seen in 2 patients to date	4/11 patients discontinued RUF, mainly due to AEs (fatigue, reduced strength and impulse). No vomiting, fever, or infections observed
Straub <i>et al.</i> , 2010	CP Germany	Adults with phar- macoresistant epilepsies (n = 85); mean age 33.4 years (range 19-68 years). 52 patients with LGS	Slow titration: +200 mg/3-7 days; target 1200-3400 mg/day	All patients: 2-4 concomitant AEDs (mean 2.0). VNS in 26 patients	Mean 18.2 months (range 3-26 months)	Assessed in 72 (44 with LGS). 26/72 patients achieved > 50% seizure frequency reduction (15/44 LGS); 11/72 achieved > 75% seizure frequency reduction. No seizure freedom observed. Seizures worsened in 1	14/85 patients had RUF-associated AEs, mainly nausea (n = 7) and sedation (n = 5). AEs led to discontinuation in 7 patients

Table 1. (Continued)

Authors	Setting	Population	Rufinamide dosing	Previous/ concomitant treatment	Follow-up	Efficacy	Tolerability
Mahendrakar <i>et al.</i> , 2010	CP (single residential care centre) UK	Children and adolescents with drug-resistant epilepsy and learning difficulties (n = 15); 8M/7F; mean age 17.4 years (range 10-21 years). 14 (93.3%) patients with LGS	Not given	All on 2-4 AEDs	Mean 6.4 months (range 3-18 months)	5/15 patients achieved > 50% seizure frequency reduction; 1 became seizure-free. No increase in status epilepticus observed. Behaviour improved in 3 patients with pre-existing behavioural problems	Well tolerated, but RUF discontinued in 6 patients, due to worsening seizures, lack of efficacy and behavioural problems. In one patient, seizures improved, but behaviour worsened, so RUF was discontinued
Nakken <i>et al.</i> , 2009	Prospective, open-label study (single centre) Norway	Children and adolescents with LGS or "LGS-like condition" (n = 19); 15M/4F; mean age 10.9 years (range 4-17)	Not given, but suggest in conclusion that higher doses could have been tried	Average of 8.7 previous AEDs tried (range 3-14). 12 patients had/were having VNS	Mean 9 months (range 0.2-13 months)	2/19 achieved > 50% seizure frequency reduction; 9/19 achieved < 50% seizure frequency reduction; 7/19 experienced no change; 1 experienced seizure aggravation. Subjective improvement reported by 5/19	AEs reported by 8/19 patients, most frequently fatigue (n = 4). 13/19 patients continued RUF treatment
Ryzi <i>et al.</i> , 2009	CP (single centre) Czech Republic	9 children with LGS; 6M/3F; age 5-18 years	Not given	5-10 previous AEDs (median 5). 3 patients received 2 concomitant AEDs; 6 received 3 concomitant AEDs	3 months	3/9 patients achieved > 50% seizure frequency reduction in 1 month and 2/9 achieved > 50% seizure frequency reduction in 3 months	5/9 reported AEs (fatigue n = 3; sleep disturbances n = 1; somnolence n = 1; unstable gait n = 1; vomiting and dysorexia n = 1)

Table 1. (Continued)

Authors	Setting	Population	Rufinamide dosing	Previous/ concomitant treatment	Follow-up	Efficacy	Tolerability
Cantarín <i>et al.</i> , 2009	Prospective, add-on, open-label study (single centre) Spain	25 (< 18 years); 15M/10F. 15 with LGS; 10 with epileptic encephalopathies with "incomplete forms of LGS"	Initiated at 10 mg/kg/day, increased by 10 mg/kg every 1-2 weeks to a maximum of 40 mg/kg/day	Mean number of previous AEDs: 7 (range 3-15). All received 3 concomitant AEDs	Mean 8 months (range 3-18 months)	3/25 patients became seizure-free; 9/25 achieved 50-99% seizure frequency reduction; 3/25 achieved 25-49% seizure frequency reduction; 5/25 no change; 5/25 worsening	18/25 patients reported AEs, generally mild and transient and most frequently somnia and vomiting. RUF was discontinued in 5 patients due to poor tolerability
Lund and Lossius, 2009	CP(single centre) Norway	Adults with LGS or "LGS-like conditions" (n = 15); mean age 32 years (range 16-57 years); 80% mentally retarded	Mean dose: 1,433 mg/day (range 400-2,000 mg/day)	Tried average of 12 AEDs (range 8-19) prior to RUF. 7 had implanted VNS. 4 had had epilepsy surgery	2 stopped treatment before 3 months. Mean follow-up was 7.2 months (range 3-13 months) in remaining patients	1/15 patient achieved > 50% seizure frequency reduction; 4/15 achieved < 50% seizure frequency reduction; 10/15 experienced no change (except transient improvement in 3)	Only 1 reported AE (tiredness)
Awadh <i>et al.</i> , 2009	CP (3 centres) Scotland	Children (n = 16) with refractory epilepsy with predominant drop attacks; 10M/6F; mean age 8 years (range 3.5-17.5 years). 5 with <i>de novo</i> LGS; 4 with cryptogenic LGS	Not given	To be included, patients had to be refractory to ≥ 3 AEDs	3-14 months	2/5 <i>de novo</i> LGS patients and 1/4 cryptogenic LGS patients achieved ≥ 50% seizure frequency with amelioration of drop attacks; improvement was seen within 3 weeks	No AEs reported

AE: adverse event; AED: antiepileptic drug; CP: clinical practice; LGS: Lennox-Gastaut syndrome; RUF: rufinamide; VNS: vagus nerve stimulation.

divided doses and increased every other day, in increments of approximately 10 mg/kg, to a target dose of 45 mg/kg/day, or 3,200 mg/day, whichever is the less, administered in two equally divided doses. It is not known whether doses lower than the target doses are effective. In adults with LGS, treatment should be initiated at 400-800 mg/day administered in two equally divided doses and increased by 400-800 mg every other day to a maximum of 3,200 mg/day administered in two equally divided doses. It is not known whether doses lower than 3,200 mg are effective (BANZEL™ PI).

Recently, results were published of a retrospective observational study conducted in a single centre in the United States (Children's Hospital Boston), in which the efficacy, tolerability and dosing schedules associated with rufinamide treatment of patients with LGS were documented (Vendrame *et al.*, 2010). Efficacy was assessed by comparing seizure frequency on rufinamide therapy (median duration of follow-up 5.2 months; range 4-10 months) with seizure frequency 3 months prior to initiation of rufinamide treatment (Vendrame *et al.*, 2010).

The study population included 26 patients with LGS, with a median age of 14 years (range 4-21 years) (Vendrame *et al.*, personal communication). In the LGS patients, rufinamide was initiated at a median dose of 9.2 mg/kg/day and the median maintenance dose was 42.1 mg/kg/day. The maximum dose was reached after a median of 78 days (range 30-180 days) (Vendrame *et al.*, personal communication). All patients with LGS received concomitant AEDs. Overall, 10/26 (38.5%) LGS patients were responders ($\geq 50\%$ seizure frequency reduction) and the median seizure frequency reduction was 50% (Vendrame *et al.*, 2010). Three patients with LGS (11.5%) experienced AEs. In two patients, these consisted of dizziness and lethargy, which led to discontinuation of rufinamide in one case. The third patient experienced a rash that was only transitory and medication was not suspended (Vendrame *et al.*, personal communication).

Several other studies conducted in the United States have assessed the efficacy and tolerability of rufinamide treatment of LGS patients in clinical practice (table 2).

Comparison of rufinamide use in clinical practice vs clinical trial

In the randomised controlled trial that formed the basis of its marketing authorisation, the maximum target rufinamide dose of approximately 45 mg/kg/day was achieved by 87.8% of patients (Glauser *et al.*, 2008). Titration took place over a maximum of 14 days, with 76.9% of patients who achieved the target dose doing so within 7 days, the remaining 23.1% achieving the

target dose in approximately 14 days (Glauser *et al.*, 2008). At the end of the titration period, rufinamide dosing was fixed for the remaining 10 weeks of the double-blind treatment period. In clinical practice, dosing is not restricted by study design issues, and is usually tailored to the individual patient's needs, based on severity of LGS, tolerability and clinical efficacy. This is reflected in the recently published accounts of using rufinamide in clinical practice (Kluger *et al.*, 2009; Vendrame *et al.*, 2010; Coppola *et al.*, 2010). In both the German/Austrian and the US studies, rufinamide was generally titrated more slowly than recommended in prescribing information. In the German/Austrian study, maximum rufinamide doses were generally achieved within 4 weeks; but in the US study, the median time to maximum dosing was approximately 11 weeks. In the German/Austrian study, rufinamide was generally initiated at 10 mg/kg/day; in the US study, the median initial dose was slightly lower than this (9.2 mg/kg/day). The final maintenance doses achieved in the clinical practice studies were a little lower than, but generally similar to, the target dose of 45 mg/kg/day used in the clinical trial.

The "slower and lower" dosing schedules employed in the clinical practice studies do not seem to have adversely affected the efficacy of rufinamide. In the 12-week randomised clinical trial, the responder rate for total seizures was 31.1% and no patients achieved seizure freedom (Glauser *et al.*, 2008). In the 12-week German/Austrian clinical practice study, the responder rate for LGS patients was 54.8% and 12.9% achieved seizure freedom during the last 4 weeks of the observation period (Kluger *et al.*, 2009), and in the US clinical practice study, the responder rate for LGS patients was 38.5% and no patients achieved seizure freedom (Vendrame *et al.*, 2010). However, it is noteworthy that the tolerability of rufinamide in clinical practice appears to have been improved by employing a lower and slower titration schedule. In the clinical trial, AEs were reported by 81.1% LGS patients treated with rufinamide (Glauser *et al.*, 2008), compared with 51.6% and 11.5% of patients in the German/Austrian and US clinical practice studies (Kluger *et al.*, personal communication; Vendrame *et al.*, personal communication). Moreover, whereas somnolence and vomiting were the two most frequently occurring rufinamide-associated AEs in the clinical trial – reported by 24.3% and 21.6% of patients – their incidence was substantially lower in the clinical practice studies. In the German/Austrian study, sleep disturbances were reported by only 9.7% of LGS patients and vomiting also by only 9.7%; the most frequently occurring AE being fatigue, reported by 12.9% of patients (Kluger *et al.*, personal communication). In the US study, AEs were reported by only 11.5% of LGS patients and consisted of dizziness and lethargy (7.7%) and rash

Table 2. Summary of additional studies conducted in the United States in which rufinamide has been used in clinical practice.

Authors	Setting	Population	Rufinamide dosing	Previous/concomitant treatment	Follow-up	Efficacy	Tolerability
Bruno <i>et al.</i> , 2009	CP (single centre) Boston, MA	Patients (n=37) with refractory tonic, tonic-clonic, atonic, atypical absence, infantile spasms and complex partial seizures; 19M/18F; mean age 12 years (range 3-37). 3 with LGS	Initiated at 5 mg/kg/day, increased by 5 mg/kg every 5 days to a maximum of 50 mg/kg/day, depending on efficacy/tolerability	Not given	Not given	~30% patients experienced a significant decrease in both the severity and frequency of seizures; 3 became seizure-free at low rufinamide doses; 2 experienced exacerbation of myoclonic seizures	AEs were rarely reported: fatigue (n=4), nausea and dizziness (n=1), blurred vision (n=1). There were no reports of vomiting, headache, or rash
Miller-Horn <i>et al.</i> , 2009	CP (single centre) Stony Brook, NY	15 patients; 10 M/5 F; age 4-51 years. 8 had LGS	Mean dose 1,120 mg/day (range 400-2400 mg/day), divided bid	All patients were receiving 1-4 concomitant AEDs; 3 had a VNS implanted	Mean 81 days (range 5-151 days)	7/15 experienced improved seizure control; 4/15 showed no improvement; 4/15 discontinued due to AEs	4/15 discontinued due to AEs (anorexia/nausea n=2; rash n=2). One patient with rash evolved into DRESS requiring high-dose prednisone

Table 2. (Continued)

Authors	Setting	Population	Rufinamide dosing	Previous/concomitant treatment	Follow-up	Efficacy	Tolerability
Ghacibeh <i>et al.</i> , 2009	CP Hackensack, NY and New York, NY	4 with generalised or mixed epilepsy syndromes. 1 (36 years) with "symptomatic generalised epilepsy not entirely consistent with LGS". 1 patient (3.5 years) with LGS	Adult: titrated to 3,200 mg/day. Child: titrated to 200 mg bid	Adult: RUF added to lamotrigine, phenobarbital and levetiracetam. Child: RUF added to levetiracetam, clonazepam, valproic acid and vigabatrin	Not given	Adult: minimal initial improvement, but after titrating to 3,200 mg/day experienced multiple daily episodes of prolonged myoclonic seizures, which persisted until RUF was partially tapered. Child: atonic seizures increased by 15-20/day; also developed "bicycling-like seizures" and convulsive seizures. Seizures returned to baseline after RUF was decreased and discontinued	Not given (other than worsening of seizures, outlined under "Efficacy")

AE: adverse event; AED: antiepileptic drug; CP: clinical practice; DRESS: drug rash with eosinophilia and systemic symptoms; LGS: Lennox-Gastaut syndrome; RUF: rufinamide; VNS: vagus nerve stimulation.

(3.8%) (Vendrame *et al.*, personal communication). It is interesting to note that, overall, rufinamide appeared to be best tolerated in the US clinical practice study, in which the slowest titration was used.

During the long-term extension to the pivotal clinical trial (median duration approximately 14.4 months), dosing could be modified, according to the investigators' discretion, to approximately 10-60 mg/kg/day; the median dose used during the trial was 52.9 mg/kg/day (Kluger *et al.*, 2010a). In the long-term follow-up of the German/Austrian clinical practice study (up to 18 months' duration), the median rufinamide maintenance dosage was 34.0 mg/kg/day in the patients with LGS (Kluger *et al.*, personal communication), considerably lower than in the long-term clinical trial. As in the short-term studies, this lower dose did not appear to adversely affect efficacy: in the long-term clinical trial, the responder rate for total seizures was 41.0% (Kluger *et al.*, 2010a), compared with 35.5% in the German/Austrian clinical practice study (Kluger *et al.*, 2010b). In the long-term Italian clinical practice study, a mean maintenance dose of 33.5 mg/kg/day rufinamide if combined with valproate and 54.5 mg/kg/day without valproate resulted in an overall responder rate of 60.5%, with 9.3% of patients achieving complete seizure freedom (Coppola *et al.*, 2010). As in the shorter-term studies, tolerability was better in the clinical practice studies than in the clinical trial extension. In the clinical trial extension, AEs were reported by 91.1% of patients and the most frequently reported AE was vomiting (30.6%) (Kluger *et al.*, 2010a). In the German/Austrian clinical practice study, AEs were reported by 61.3% of LGS patients (including the initial 12-week period), the most frequently reported being fatigue (12.9%) and sleep disorder (12.9%), with vomiting only reported by 9.7% of patients (Kluger *et al.*, personal communication). In the Italian clinical practice study, AEs were reported by only 23.2% of patients and although vomiting and/or gastrointestinal disorders were the most frequently reported AEs, these were only reported by 13.5% of patients (Coppola *et al.*, 2010). This difference in tolerability is also reflected in the retention rates: 33.9% in the clinical trial extension, compared with 51.6% for LGS patients in the German/Austrian clinical practice study (Kluger *et al.*, 2010a, 2010b).

In the randomised 12-week clinical trial, the most frequently used concomitant AEDs in patients treated with rufinamide were valproate (59.5%), lamotrigine (40.5%), topiramate (27.0%), clonazepam (18.9%) and carbamazepine (16.2%) (Glauser *et al.*, 2008). In the long-term extension of the clinical trial, these were also the most frequently used concomitant AEDs (Kluger *et al.*, 2010a). In the initial 12-week period of the German/Austrian clinical practice study, the most frequently used concomitant AEDs in LGS

patients were valproate (54.8%), levetiracetam (25.8%), clobazam (19.4%), topiramate (19.4%) and bromide (19.4%) (Kluger *et al.*, personal communication), and, in the long-term extension of the study (including the initial 12-week period), the most frequently used AEDs were valproate (54.8%), levetiracetam (25.8%), lamotrigine (22.6%), clobazam (19.4%), topiramate (19.4%), oxcarbazepine (19.4%), zonisamide (19.4%) and bromide (19.4%) (Kluger *et al.*, personal communication). In the Italian clinical practice study, the most frequently used concomitant AEDs were valproate (69.8%), levetiracetam (39.5%), clonazepam (20.9%) and lamotrigine (20.9%) (Coppola *et al.*, 2010). In the US clinical practice study, the use of concomitant AEDs was higher than in Europe, with approximately one-half to two-thirds of LGS patients receiving benzodiazepines (69.2%), levetiracetam (65.4%), valproate (61.5%), zonisamide (61.5%) and lamotrigine (57.7%) (Vendrame *et al.*, personal communication). It should be noted that patients were excluded from the clinical trial if they were taking more than three concomitant AEDs (Glauser *et al.*, 2008), but 15.4% of LGS patients in the US clinical practice study were taking more than three concomitant AEDs (Vendrame *et al.*, 2010).

The design of the randomised controlled trial was by necessity strictly controlled, in terms of inclusion/exclusion criteria, a fixed titration schedule with single target dose based on body weight, and the requirement that concomitant AEDs (and their doses) could not be changed. By contrast, the clinical practice studies were open, and afforded much greater flexibility to the clinician in terms of dosing and other treatment decisions, which may have resulted in a degree of clinician bias. Such differences in study design are likely to have had an impact on the outcomes observed in the clinical study versus the clinical practice studies.

Rufinamide in clinical practice: case reports

The diverse features and characteristics of LGS require a flexible, individualised approach to treatment in clinical practice. Here, we present case reports that describe the use of adjunctive rufinamide in seizures associated with LGS, including patients predominantly experiencing drop attacks (Case Reports 1 and 2), a patient experiencing atypical absences, myoclonic seizures and non-convulsive status epilepticus (Case Report 3), and a patient with epileptic encephalopathy involving focal seizures (Case Report 4). These cases not only demonstrate the diversity of LGS, but also highlight the challenges involved in recognising LGS as it develops and evolves, and the requirement for a flexible and adaptive approach to its treatment and management.

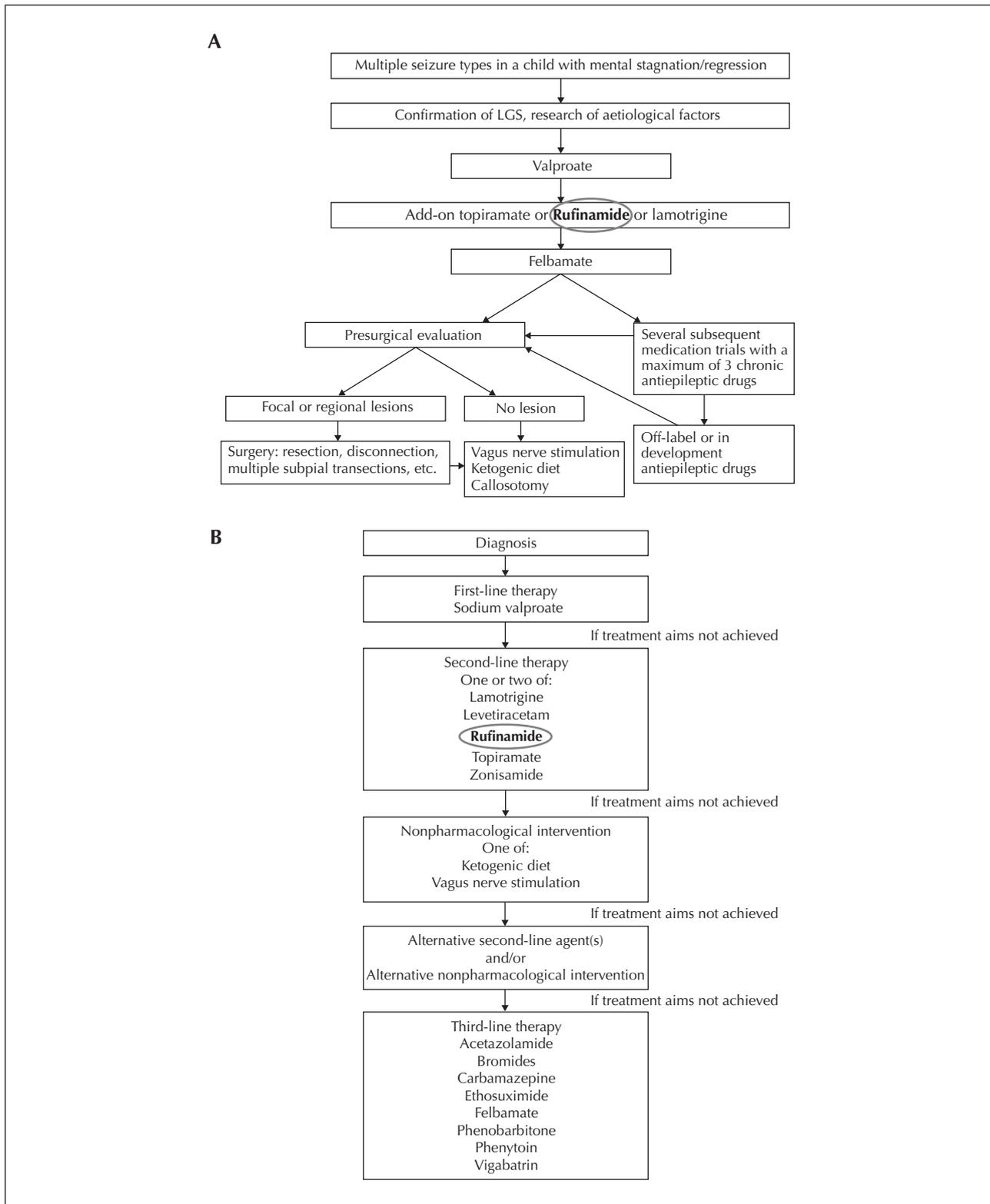


Figure 2. Position of rufinamide in recently published algorithms: **(A)** treatment strategy for children with highly pharmacoresistant seizures (reprinted from van Rijckevorsel, 2008 with permission from Dove Medical Press Ltd) and **(B)** recommended Lennox-Gastaut syndrome treatment algorithm* (reprinted from Ferrie and Patel, 2009 with permission from Elsevier).

* Only lamotrigine, topiramate, rufinamide and felbamate (only in the United States) are approved for treatment of seizures associated with LGS.

The place of rufinamide in current treatment guidelines/algorithms

In 2004, the American Academy of Neurology published guidelines for the use of (then) new AEDs in the treatment of refractory epilepsy, which recommended that topiramate and lamotrigine may be used to treat drop attacks in paediatric and adult patients with LGS (French *et al.*, 2004). A 2003 Cochrane review of randomised controlled trials of treatments for LGS (reassessed in April 2009) concluded that lamotrigine, topiramate, felbamate and rufinamide might be helpful as adjunctive therapy for LGS (Hancock and Cross, 2009). In a survey of 39 US paediatric specialists, published in 2005, valproate was indicated as the first choice for first-line treatment of LGS, with topiramate and lamotrigine also considered first-line treatment options (Wheless *et al.*, 2005). Similarly, in a survey completed by 42 European specialists, conducted in 2007, valproate was considered to be the first-line treatment of choice, with lamotrigine and topiramate also indicated as first-line options (Wheless *et al.*, 2007).

More recently, a consensus of expert opinion recommended that, based on clinical experience and evidence from class III or IV studies, AEDs with a broad spectrum – such as valproate, benzodiazepines and lamotrigine – should be used at an early stage of LGS, when drop attacks are the predominant seizure type, since such agents might also be effective in treating atypical absence seizures. During the state (as opposed to onset) stage of the disorder, the paper recommended that lamotrigine, topiramate, felbamate and rufinamide should be considered for the treatment of drop attacks (Arzimanoglou *et al.*, 2009).

Other recently published treatment algorithms have recommended the use of first-line therapy with valproate, together with adjunctive therapy with either topiramate or lamotrigine or rufinamide, followed by felbamate (van Rijckervorsel, 2008), or one or two of lamotrigine, topiramate, rufinamide, levetiracetam and zonisamide (Ferrie and Patel, 2009) (*figure 2*).

As discussed elsewhere in this supplement (“All children who experience epileptic falls do not necessarily have Lennox-Gastaut syndrome LGS... but many do”), a key aspect in ensuring successful treatment of LGS is its diagnosis. Definitions used in clinical trials are by necessity strict, but, in clinical practice, the borders of LGS are more imprecise and it is often difficult to differentiate LGS from other symptomatic or cryptogenic generalised epilepsies. Based on clinical, EEG and/or historical features, it is important to use appropriate treatments as early as possible and potentially improve prognosis. It should be noted that rufinamide is only approved for adjunctive treatment of seizures associated with LGS in patients 4 years of age and older.

Conclusion

Current evidence from clinical trials and clinical practice studies indicates that rufinamide is an effective and well-tolerated adjunctive treatment for seizures associated with LGS. Although treatment guidelines are useful in summarising clinical evidence, particularly relating to safety issues that may not become apparent during relatively short-term regulatory trials (e.g. rare AEs, aggravation of particular seizure types), treatment decisions are largely based on physicians' individual clinical experience, together with drug availability. In the case of rufinamide, which has only been licensed for a few years, clinical experience is currently at an early stage, and there are still a number of important questions to be answered, including: whether there are specific drug sequences and/or drug combinations with rufinamide that are particularly beneficial for LGS patients; how patients who may not show the expected response to rufinamide should be managed (e.g. whether the dose should be increased, if tolerated; whether concomitant AEDs should be changed; whether rufinamide should be re-tried at a later stage in patients who tolerated but did not initially respond to it); and how early in the course of LGS adjunctive treatment rufinamide should be initiated (e.g. whether rufinamide should be used to treat particular seizure types, such as drop attacks). The place of rufinamide in the adjunctive treatment of LGS is therefore likely to evolve as experience builds and as further evidence-based data emerge. □

Disclosure.

Preparation of this manuscript was supported by Eisai through mXm Medical Communications.

A. Arzimanoglou declared having received consultancy fees and/or research grants from Cyberonics, Eisai, GlaxoSmithKline, Pfizer and UCB Pharma.

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Case report 1

Robert Flamini

The patient was a 7-year-old girl, weighing 22 kg, who was aged 2 years at seizure onset and diagnosed with LGS aged 4 years. Seizure semiology evolved into a combination of tonic drop attacks and atypical absences. Drop attacks consisted of tonic extension of the proximal upper limbs, elevation of shoulders, abduction of the arms and head drop, lasting approximately 15-20 seconds. Atypical absences were clinically described as staring and unresponsiveness. The patient also experienced partial seizures, characterised by prolonged staring, lasting approximately 2 minutes. Seizure attacks occurred daily and drop attacks were the most prevalent seizure type at the time when rufinamide treatment was initiated. EEG assessment in 2004 demonstrated occasional small amplitude left temporal and left frontal spikes, and left hemisphere slowing, with bifrontal spikes appearing later on. In 2006, EEG (including video assessment) showed background slowing, multifocal interictal discharges, generalised SSW complexes, epochs of electrodecrement, and tracing consistent with LGS. In 2010, EEG still shows features of LGS, though the amount of interictal discharges has decreased. Magnetic resonance imaging conducted in 2004 (at first acute presentation) showed a mild increase in cortical signalling. Approximately 5 months later, it showed diffuse cerebral atrophy and thereafter the findings were similar, with atrophy worse on the left side than the right. Extensive metabolic and infectious work-ups were negative. LGS aetiology was presumed to be encephalitis. The patient demonstrated global developmental delay, with a significant delay in expressive speech. She had also developed a behavioural disorder, characterised by impulsivity, inattention and aggression.

Prior to initiation of rufinamide, treatment consisted of lamotrigine (partial response), levetiracetam (no response), topiramate (partial response), valproate (improvement in seizure frequency, but not seizure-free) and ketogenic diet (no response). Rufinamide was initiated at 10 mg/kg/day, with gradual escalation over 4 weeks to 30 mg/kg/day. Concomitant AEDs at the time of rufinamide initiation were lamotrigine (50 mg qam; 75 mg qhs) and valproic acid (125 mg tid). There was a dramatic reduction in seizure frequency at 10 mg/kg/day (~75% improvement). At 30 mg/kg/day, the patient became seizure-free and she has remained seizure-free at this dose for approximately 1.5 years. This allowed polytherapy to be simplified, since lamotrigine was discontinued a few months later because of the good response to rufinamide. The patient continued to receive rufinamide (30 mg/kg/day) and valproic acid (250 mg qam, 125 mg qpm, 250 mg qhs). Other treatments for behaviour have been tried without interactions. There were no rufinamide-associated side effects. This patient with previously intractable drop attacks therefore experienced an excellent response to rufinamide that appeared at a low dose early in the treatment phase and has persisted over time.

Case report 2

Trevor Resnick

The patient was an 11-year-old boy, weighing 27 kg, with seizure onset at 6 months. LGS, of cryptogenic aetiology, was diagnosed at 3 years of age. The predominant seizure types were tonic and atonic seizures. At 6 months, seizures manifested as head drops, which responded to treatment with phenobarbital. The patient remained seizure-free without medication until age 5 years, when intractable tonic seizures (1-2 times/day) and atonic drop attacks (10-20 per day) developed. EEG and video-EEG demonstrated SSW complexes, background slowing, multifocal spikes, 10 Hz fast frequencies and electrodecrements (*figure 3*). Physical examination showed the patient to be non-stigmatised, normocephalic and non-focal, with poor coordination. MRI was normal, metabolic testing was negative, but microarrays revealed an abnormality on chromosome 15-758.9. The patient has demonstrated developmental delay, with hypotonia, poor coordination and an IQ of 50. He did not walk until aged 2.5 years, spoke no words until age 5 years, and was home schooled because of frequent seizures.

Prior to initiation of rufinamide, treatment consisted of lamotrigine (no response), levetiracetam (no response), valproate (no response), zonisamide (no response) and ketogenic diet (no response). Rufinamide was initiated as add-on therapy to topiramate (100 mg bid) and clobazam (10 mg tid) at a dose of 10 mg/kg/day, increased weekly by 10 mg/kg to a final dose of 35 mg/kg/day. Seizure frequency was reduced by 50% for 6-8 weeks without side effects, but relapsed to baseline levels after 8 weeks. Rufinamide was increased to 45 mg/kg/day, but this made no difference. There were no rufinamide-associated side effects. This case therefore illustrates that some patients showing an initial response may develop tolerance to rufinamide; it also illustrates that there may be some patients who do not respond to any treatment.

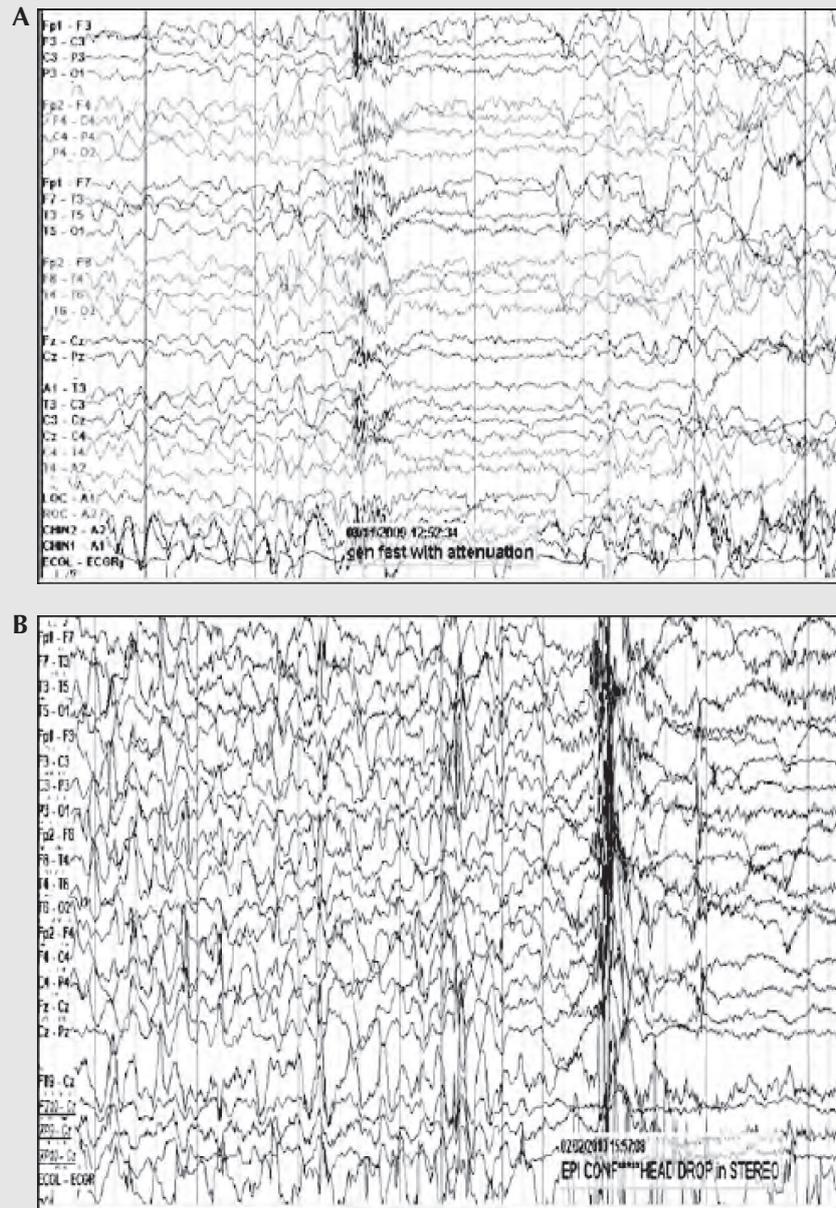


Figure 3. A) EEG during a tonic drop. B) EEG during a tonic head drop.

Case report 3

Lawrence Brown

This patient was a 17-year-old boy, who experienced onset of seizures at age 11 months. Seizure semiology consisted of head nods to the left side associated with upward eye deviation and eye flutter (starting at 11 months), drop attacks and staring spells. The patient experienced approximately 50 atonic-tonic seizures per day in clusters, lasting from 30 seconds to several hours. Although MRI was initially normal, frontal lobe arteriovenous malformation was discovered at age 8 years during the fourth MRI in 7 years. This consisted of an 8 mm area of signal abnormality in the left superior frontal gyrus, highly indicative of a tumour (*i.e.* ganglioglioma or dysembryoplastic neuroepithelial tumour was more likely than a vascular anomaly). Resective surgery in 2002 (age 8-10 years) was unsuccessful in controlling seizures. Subsequent MRIs showed no new lesions, only the surgical resection. The patient developed cognitive impairment and behavioural disturbances comprising hyperactivity, frequent tantrums and aggression. LGS diagnosis was made at age 10 years, with video-EEG confirmation of multifocal and generalised spike-wave abnormalities and clinical-electrographic seizures characterised by eye flutter and head nods.

Prior to rufinamide, treatment consisted of valproate (diarrhoea on repeated trials; thrombocytopenia), topiramate (ineffective; sedation), zonisamide (ineffective), phenobarbital (ineffective, sedation), phenytoin (ineffective), lamotrigine (incompletely effective), clonazepam (ineffective; poor behaviour), ethosuximide (transient improvement, then ineffective), ketogenic diet (ineffective), levetiracetam (ineffective: aggression), vagus nerve stimulation (implanted April 2004; ineffective) and clobazam (ineffective). At the time of starting rufinamide therapy, the patient was receiving topiramate (150-100-150 mg; 8 mg/kg/day), lamotrigine (100 mg tid; 6 mg/kg/day), clobazam (10 mg bid; 0.4 mg/kg/day) and vagus nerve stimulation (30 s on, 1.8 min off; output current 1.5 mA; frequency 20 Hz; pulse width 250 μ s). Rufinamide was initiated at 400 mg bid for 1 week, uptitrated to 800 mg bid for 1 week and then uptitrated to 1,200 mg bid. Seizure frequency, severity and duration of all types (including eye flutter, head nods and atypical absence) were decreased by 50%, and seizures were mostly limited to early morning hours. This was accompanied by a marked progression in speech, fine motor skills and academic performance. Subsequently, clobazam was withdrawn as rufinamide treatment built up, topiramate was decreased to 100 mg tid (6 mg/kg/day), and rufinamide was increased to 800-800-1,000 mg (72 mg/kg/day) with further improvement. This case illustrates that even the most refractory patients may respond to a new treatment. It also highlights that dosing guidelines are just guidelines: a response can be achieved using higher dosing, as long as response is balanced against side effects and the treatment regimen is simplified by eliminating ineffective therapies.

Case report 4

Sanjeev Kothare



Figure 4. EEG showing slow spike-wave discharges.

The subject is a 5-year-old boy with polymicrogyria and multiple seizure types since birth. The semiology of seizures described by family and caregivers included clonic and tonic jerks of one leg/arm, staring and twitches of the eyelids, and atonic seizures (drop attacks). Long-term monitoring using video-EEG showed frequent electroclinical seizures, with onset in the bilateral centroparietal regions, clinically associated with eyelid fluttering, bobbing of eyeballs, or head jerks. Interictally, there were frequent bilateral centroparietal sharp waves and right centroparietal sharp waves, and occasional right posterior temporal sharp waves. Sleep-potentiated diffuse sharp waves (centroparietal maximum) with a spike index of 83, without fulfilling electrical status epilepticus during slow sleep (ESES) criteria, were noted during the study (*figure 4*). Brain MRI showed perisylvian polymicrogyria with extensive frontal, parietal and temporal lobe involvement bilaterally. Seizures occurred in 1-8 clusters, approximately 1-2 times per day. Diagnosis of LGS was made at age 1 year, based on seizure semiology and EEG characteristics. Prior AEDs included lamotrigine, zonisamide, and topiramate. Rufinamide was added to levetiracetam, valproate, and clonazepam at a dose of 100 mg bid and increased to a maximal dose of 400 mg/day (40 mg/kg/day) within 1 month. At this dose, approximately 1-2 clusters of seizures were reported per day. Rufinamide was therefore increased to 600 mg/day (60 mg/kg/day). At this dose, after 4 months of therapy, no further seizures were reported. No side effects were reported, despite concurrent therapy with valproate. Clonazepam was tapered off over 1 month. Therefore, in this case of LGS secondary to polymicrogyria, the patient showed a dramatic response to rufinamide, with complete resolution of atonic drop attacks. Specifically, resolution of seizures was achieved at a slightly higher dose of 60 mg/kg/day, with no side effects, and complete seizure control at 4 months' follow-up.