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Dosing considerations for rufinamide in patients with Lennox–Gastaut syndrome: Phase III trial results and real-world clinical data

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ABSTRACT

Purpose: Lennox–Gastaut syndrome (LGS), a rare, severe form of childhood-onset epilepsy, is difficult to control. Rufinamide is indicated for adjunctive treatment of seizures associated with LGS in adults and pediatric patients aged ≥1 year. In clinical practice, rufinamide dosing and titration may differ from the trial setting. Here, rufinamide clinical trial data are compared with real-world experience to provide insight into optimal dosing and titration strategies.
Methods: Rufinamide Phase III and open-label extension (OLE) studies were reviewed; effect of titration and dose on adverse events (AEs) and concomitant AED use were analyzed. Real-world studies of rufinamide in LGS were identified via PubMed search. Clinical data were extracted and compared.
Results: Results demonstrated that a rapid titration schedule (7 or 14 days) of rufinamide was tolerable for most patients and resulted in highly significant reductions in total and tonic–atonic seizures, with efficacy and tolerability sustained over 3 years. The most common AEs during the Phase III study – somnolence, vomiting, and pyrexia – occurred during the first 3 weeks of treatment, and a small subset of patients were unable to reach target dose in that time. Use of concomitant AEDs had no clinically significant effect on plasma concentrations of rufinamide. Data from real-world clinical studies are consistent with the Phase III and OLE study results. However, relative to those used in clinical trials, lower doses and slower titration schedules were commonly employed in real-world settings.
Conclusions: A lower dose and slower titration schedule ("low and slow") may reduce incidence of AEs without compromising efficacy of rufinamide in LGS.

1. Introduction

Lennox–Gastaut syndrome (LGS) is one of the most severe forms of childhood-onset epilepsy, accounting for approximately 1% to 4% of all childhood epilepsy cases, with peak onset occurring between the ages of 3 and 5 years [1–3]. Although the etiology of LGS is frequently unknown, the condition is characterized by a triad of symptoms, including impairment of cognitive function, slow spike-and-wave complexes on electroencephalogram (EEG) recordings, and multiple seizure types, making it particularly difficult to control [1,3]. Combinations of antiepileptic drugs (AEDs) have commonly been used in an attempt to achieve seizure control in these patients [1].

The goal of treatment for LGS is reduction of seizures to the greatest extent possible while limiting adverse events (AEs),

Abbreviations: AE, adverse event; AED, antiepileptic drug; AUC, area under the curve; BID, twice daily; C_{max}, peak plasma concentration; ECG, electrocardiogram; EEG, electroencephalogram; EMA, European Medicines Agency; FDA, Food and Drug Administration; GI, gastrointestinal; ICF, International Classification of Functioning, Disability and Health; LGS, Lennox–Gastaut syndrome; OLE, open-label extension; PD, pharmacodynamic; PK, pharmacokinetic; RFM, rufinamide; SAE, serious adverse event; SS, steady state; TID, thrice daily; T_{max}, time to maximum plasma concentration.

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ultimately providing the patient with the best possible quality of life [4]. Pharmacotherapies for the treatment of LGS include rufinamide, clobazam, valproate, lamotrigine, topiramate, felbamate, zonisamide, and levetiracetam [5]. Rufinamide, a triazole derivative structurally dissimilar to other AEDs, is indicated for the adjunctive treatment of seizures associated with LGS in pediatric patients 1 year of age and older as well as in adults [6]. Available pharmacokinetic (PK) and pharmacodynamic (PD) analyses have demonstrated a positive correlation between plasma rufinamide concentrations and improved seizure control, although AEs are also more likely in patients with higher rufinamide plasma concentrations [7].

In general, rufinamide has a mild side-effect profile and a relatively low potential for drug–drug interactions. The primary clinically relevant drug–drug interaction is with valproate, which substantially decreases the clearance of rufinamide [8]. Decreased serum levels of rufinamide are observed when it is coadministered with phenytoin, phenobarbital, primidone, carbamazepine, and vigabatrin [7,8]. In addition, rufinamide decreases the plasma concentrations of carbamazepine and lamotrigine by 7% to 13%, and increases plasma levels of phenobarbital by 8% to 13% and phenytoin by 7% to 21% [6,7].

The half-life of rufinamide is relatively short, 6 to 10 h, and plasma rufinamide concentrations rise slowly – time to maximum plasma concentration (T_{max}) is approximately 4 to 6 h – which minimizes fluctuations in plasma concentrations with twice-daily (BID) dosing [7]. Steady-state (SS) exposure to rufinamide, whether described as peak plasma concentration ($C_{max,SS}$) or area under the curve for 12-h dosing ($AUC_{0-12,SS}$), increases at a rate that is less than dose-proportional. Rufinamide is absorbed well when taken with food, which increases C_{max} and AUC, but has no effect on T_{max} [7].

In the United States, the Food and Drug Administration (FDA)-recommended starting dose for rufinamide in pediatric patients (1 to <17 years of age) with LGS is approximately 10 mg/kg, administered in two equally divided doses. This dose may be increased by 10 mg/kg every other day, up to a maximum dose of 45 mg/kg, not to exceed 3200 mg/day [6]. For adults ≥17 years, treatment should be initiated at 400 to 800 mg/day administered in two equally divided doses, with dose increases of 400 to 800 mg every other day up to a maximum dose of 3200 mg/day [6]. The European Medicines Agency (EMA) recommends an initial dose of 200 mg daily in children ≥4 years old and <30 kg not receiving valproate; the dose may be increased by 200 mg/day as frequently as every 2 days, to a maximum dose of 1000 mg/day [9]. An initial dose of 400 mg/day is recommended for adults, adolescents, and children ≥4 years of age (≥30 kg), with 400 mg/day dose increases, as frequently as every 2 days, up to a maximum daily dose based on body weight as follows: 1800 mg/day for patients weighing 30.0–50.0 kg, 2400 mg/day for those weighing 50.1–70.0 kg, and 3200 mg/day for those weighing ≥70.1 kg [9]. The US and EMA labels both recommend lower starting doses for pediatric patients simultaneously receiving valproate, and the FDA also recommends a lower starting dose in adult patients receiving valproate [6,9].

Rufinamide's efficacy in LGS was demonstrated in a pivotal Phase III double-blind, placebo-controlled trial and open-label extension (OLE) study [10,11]. The use of rufinamide to treat patients with LGS in clinical practice has also been described, providing additional data on more flexible dosing schedules and outcomes. Here, real-world and clinical data will be considered with regard to dosing/titration vs. AE patterns, concomitant AED use, and dosing for both pediatric and adult patients with LGS to provide insight into best clinical practices.

2. Methods and patients

2.1. Phase III pivotal trial and open-label extension

The Phase III double-blind, placebo-controlled pivotal trial (core study) was 84 days in duration, and involved 138 patients with LGS, 4–30 years old (median 12 years), who were randomized to receive either rufinamide ($N = 74$) or placebo ($N = 64$) [11]. The long-term OLE of the double-blind study involved 124 patients who participated for a median duration of 432 days (range 10–1149 days) [10].

Study designs for the core and extension studies have been previously described. Eligibility criteria for the core study required a history of multiple seizure types, including atypical absence seizures and tonic–atonic ("drop attack") seizures, having ≥90 seizures in the preceding month, EEG evidence of a pattern of slow spike-and-wave complexes, and use of 1 to 3 concomitant fixed-dose AEDs at baseline [11]. After a 28-day baseline period, patients entered a 14-day titration period, followed by a 70-day maintenance period, for a total double-blind study period of 84 days [11]. Patients were given a starting dose of approximately 10 mg/kg/day, with a dosing target of 45 mg/kg/day or the maximum daily dose by patient weight (Table 1), whichever was less [11]. Dose titration was undertaken according to the schedule shown in Table 1.

The OLE study titration schedule for patients who received placebo during the core study and were switched to rufinamide was similar to that of the core study. These patients initiated rufinamide treatment at 10 mg/kg/day and increased to approximately 25–60 mg/kg/day in 1–2 weeks [10]. Dosing of rufinamide for all patients could be modified at the investigator's discretion to a range of approximately 10–60 mg/kg/day, given as BID or thrice-daily (TID) doses [10].

2.2. Real-world data: Literature search strategy

The literature search to develop background for this article was based on articles in English found on PubMed up to June 2015. The primary search terms were "rufinamide," AND "pediatrics," OR "adults," OR "titration," OR "dose," AND "Lennox–Gastaut syndrome." Additional information from treatment in other epilepsy syndromes was garnered using the search terms: "rufinamide," AND "pediatrics," OR "adults," OR "titration," OR "dose," NOT "Lennox–Gastaut syndrome." Only articles in English and human studies were included. Articles of interest were initially reviewed as abstracts, and examined in their entirety when

Table 1
Rufinamide dosing schedule during core study [11].

Trial day (titration phase)	Approximate dose (mg/kg/d)	Actual dose by body weight (mg/d)			
		18.0–29.0 kg	29.1–50.0 kg	50.1–70.0 kg	>70.0 kg
1–2	10	200	400	600	800
3–4	20	400	800	1200	1600
5–6	30	800	1200	1800	2400
7	45	1000	1800	2400	3200