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Retention rates of rufinamide in pediatric epilepsy patients with and without Lennox–Gastaut Syndrome

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Summary

Objective—To evaluate the effectiveness of rufinamide (RFM) in patients with Lennox–Gastaut Syndrome (LGS) compared to those with other epilepsy syndromes using time to treatment failure (retention rate) as the outcome measure.

Methods—In this retrospective cohort study, characteristics and outcomes of all patients receiving RFM in 2009 and 2010 were recorded. The primary outcome measure was RFM failure, defined as discontinuation of RFM or initiation of an additional antiepileptic therapy. The secondary outcome measure was discontinuation of RFM. Kaplan–Meier method survival curves were generated for time to RFM failure, for all patients and by the presence or absence of Lennox Gastaut Syndrome (LGS). The impact of age, seizure type, fast or slow drug titration, and concomitant therapy with valproate on retention rate were evaluated using Cox regression models.

Results—One hundred thirty-three patients were included, 39 (30%) of whom had LGS. For all patients, the probability of remaining on RFM without additional therapy was 45% at 12 months and 30% at 24 months. LGS diagnosis was an independent predictor of time to RFM failure (HR 0.51, 95% CI 0.31–0.83), with a median time to failure of 18 months in LGS compared to 6 months in all others ($p = 0.006$).

Conclusions—In a broad population of children with refractory epilepsy, around half will continue taking the medication for at least a year without additional therapy. Patients with LGS

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Authors' contributions

SKK: study design, data collection, data analysis and interpretation, manuscript writing and revision. AM: study design, data collection, data analysis and interpretation, manuscript revision. AC: study design, analysis and interpretation of the data, manuscript revision. DD: study design, data interpretation, manuscript revision.

Conflict of interest

The authors have no conflicts of interest to disclose relevant to this research.

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are two times more likely to continue RFM without additional therapy compared to those without LGS.

Keywords

Antiepileptic drug; Refractory epilepsy; Effectiveness; Efficacy; Tolerability; Retention rate

Introduction

The new antiepileptic drug Rufinamide (RFM) gained U.S. Food and Drug Administration approval in November 2008 for adjunctive therapy of generalized seizures associated with Lennox–Gastaut Syndrome (LGS) in patients 4 years and older, with evidence of efficacy from a 3 month randomized controlled trial in LGS patients (Glauser et al., 2008). Since then, a number of studies have investigated the efficacy of RFM in children with other epilepsy types as well, including epileptic spasms and refractory epilepsy more generally (Coppola et al., 2014, 2013, 2011, 2010; Grosso et al., 2014; Joseph et al., 2011; Kim et al., 2013, 2012; Kluger et al., 2010a; Mueller et al., 2011a,b; Olson et al., 2011; Thome-Souza et al., 2014). In addition, RFM now has an indication for adjunctive therapy in refractory partial seizures in adults and adolescents (Brodie et al., 2009). However, previous retrospective post-marketing RFM studies have frequently been limited by short follow up times, outcomes assessed at variable time points, and sample sizes too small to allow adequate comparison across epilepsy syndromes.

An emerging method to address the difficulties of outcome assessment in retrospective epilepsy studies, where seizure counts may not be reliably obtained, is AED retention rate, which has gained interest as an effectiveness outcome measure in epilepsy treatment because it reflects both efficacy and tolerability, and has applicability in clinical practice (Ben-Menachem et al., 2010). One method of measuring retention rate is time to treatment failure, or the time from initiating an AED until the time it is stopped or another treatment is instituted (Ben-Menachem et al., 2010; Novy et al., 2013).

The aim of this study was to evaluate whether RFM is more effective (efficacious and tolerable) in patients with LGS than patients with other refractory epilepsy syndromes, using retention rate (time to treatment failure) as the outcome measure. In addition, we describe RFM use at a large pediatric epilepsy referral center in the first two years of its availability, and evaluate the impact of predominant seizure type, fast or slow drug titration, and concomitant therapy with valproate, a frequently used AED in this population which has known drug interactions with RFM, on RFM retention rate.

Methods

Subjects

We conducted a single-center retrospective cohort study. This study was approved by the institutional review board of the Children’s Hospital of Philadelphia (CHOP). The electronic medical records for all patients with outpatient visits in the CHOP Division of Neurology were queried for the presence of “rufinamide” or “banzel” in the medication history or

active medication list. All providers in the Division, including those in satellite practices, utilize the electronic medical record system for medication prescribing and record keeping. Inclusion criteria included at least one prescription for RFM recorded in the outpatient medical record, with the first prescription dated between January 1, 2009 and December 31, 2010. Subjects were excluded from further data collection and analysis if they had only a single second opinion visit where no follow up information was available, or there were any notations that the patient received no doses of RFM despite having received a prescription.

Patient charts were reviewed systematically for demographic and clinical data including age at seizure onset, and age at RFM initiation, sex, seizure types, epilepsy syndromes, epilepsy etiology, as well as antiepileptic treatment history and concomitant treatment, rufinamide titration schedule, initial target dose, highest total daily dose, start date and length of use, reason for discontinuation, and adverse effects. Epilepsy syndrome classification was in accordance with International League Against Epilepsy (ILAE) guidelines (ILAE, 1989) – and was determined for each patient in this study by one study member (SK) based on available clinical and electrographic information, and blinded to RFM treatment length. Study data were collected and managed using REDCap electronic data capture tools hosted at CHOP (Harris et al., 2009).

Definitions

RFM start date was defined as the date of the first RFM prescription. Initial target dose was defined as the target dose during the initial titration period (generally the dose specified on the initial prescription). RFM failure for survival analysis for the primary outcome was defined as discontinuation of RFM, initiation of another antiepileptic treatment (antiepileptic drug, the ketogenic diet, vagus nerve stimulator, or epilepsy surgery) in addition to RFM, or increase in concomitant AED dose. For the secondary outcome, RFM failure was defined as RFM discontinuation. The date of RFM discontinuation (if applicable) was defined as the day the patient's caregiver was given a weaning schedule for drug discontinuation, either during a clinic visit or during a telephone or email contact with a provider. The date of RFM failure for patients who did not discontinue RFM was defined as the date that another antiepileptic treatment was initiated. For all other subjects, observations were censored on May 5, 2011, with the last observation carried forward to this date as long as the last observation was within 6 months of this date. For those who were seen more than 6 months before May 5, 2011, the censor date was chosen as 6 months from the last contact. The last observation carried forward to a 6 month time point was chosen to avoid underestimates of time (if subjects were censored at time of last visit), and overestimates of time (assumptions about subjects seen more than 6 months ago are likely to be inaccurate, because in general refractory epilepsy patients are seen no less often than every 6 months in this practice). Reasons for failure (efficacy, tolerability, or both) were based on notations in the clinical records; designation as efficacy failure required that the patient was treated with the target dose for at least 1 week. Because of the poor reliability of efficacy data (seizure counts) based on retrospective clinical reporting, no additional efficacy information was collected except for the number of patients noted to be seizure free for greater than 6 months. Prior AED exposures were grouped into categories (2 or fewer, 3–5, or 6 or greater).

Statistical analyses

Statistical analyses were conducted in STATA version 10 (StataCorp, College Station, TX). Demographic and baseline epilepsy characteristics were summarized by standard descriptive measures. Kaplan–Meier curves were generated for the time to RFM failure (defined as specified above) for all subjects. Subsequently, separate Kaplan–Meier curves were generated for time to RFM failure for patients with LGS and those with all other diagnoses, and these plots were compared using the log rank test. A Cox proportional hazards model was developed to assess the influence of the following potential risk factors on time to treatment failure (determined a priori), adjusting also for the demographic factor age at RFM initiation: epilepsy syndrome (LGS versus all others), the presence of atonic or tonic seizures, concomitant administration of VPA, and fast (less than 2 weeks) versus slow (greater than 2 weeks) titration schedule.

Covariates were considered for inclusion in the final hazard model on the basis of an unadjusted association with RFM failure ($p < 0.25$). Effect modification was tested by including main effects and interaction terms in the Cox models. Confounding was assessed by evaluating the association of each covariate with the exposure (LGS diagnosis) and the outcome (RFM failure), and by assessing whether inclusion in the model affected the hazard ratio (HR). All analyses were 2-sided with a p value less than 0.05 considered statistically significant.

Sample size considerations

With a median time to RFM failure of 12 months, a fixed sample size of 135 subjects, and a 2:1 ratio between patients without LGS and those with LGS, we had 80% power to detect an HR for time to RFM failure of less than 0.4 or greater than 2.5 among patients for each group, and a 2 sided alpha level of 0.05.

Results

Characteristics of the cohort

One hundred forty patients were identified whose medication history listed RFM. Of these, two were being continued on the medication after starting it in the context of a clinical trial. Three patients were seen for a single second opinion visit and no follow up information was available. Two other patients were prescribed RFM but did not start using it (one for insurance reasons, one for patient refusal). Thus, 133 patients were available for analysis.

The clinical characteristics of the cohort are shown in Table 1. The median age at RFM initiation was 10 years (IQR 6–16 years). The median age at epilepsy onset was 12 months (IQR 4–26 months). Median follow up time after RFM initiation was 20 months (range 8–30 months). Number of seizure types at the time of RFM initiation was 1 in 34 (26%), 2 in 58 (43%), 3 in 31 (23%), and more than 3 in 11 (8%). Mechanism of seizure onset was generalized in 49 (37%), focal in 31 (23%), both focal and generalized in 50 (38%), and unknown/indeterminate in the remaining 3 (2%).

Electroclinical syndrome diagnosis was LGS in 41 (30%), West Syndrome in 9 (7%), Severe Myoclonic Epilepsy of Infancy (Dravet Syndrome) in 3 (2%), other syndromes in 4 (3%), and no identifiable syndrome in 78 (58%). Epilepsy etiology was unknown in 70 (52%), acquired in 8 (6%), and inborn/genetic in 57 (42%). The most common etiology, cerebral malformations, occurred in 40 (30%) patients. Epilepsy etiology is summarized in Table 2.

Median time for titration to the initial target dose was 3 weeks (range 1–8 weeks). Titration to target dose was less than 2 weeks in 39 patients, and greater than 2 weeks in 94 patients. The median target dose was 33 mg/kg/day (range 5–65). The median highest daily dose was 45 mg/kg/day (range 5–105). The median highest daily dose in patients also taking VPA (46 mg/kg/day) was not statistically significantly higher than the median highest daily dose in those not taking VPA (41 mg/kg/day, $p = 0.16$). Of the five patients whose target doses were less than 10 mg/kg/day, 2 were late adolescents of adult size, and 3 were noted to have a history of extreme sensitivity to medication side effects as the explanation for low target dose. The total daily target dose for these five patients ranged from 100 mg to 400 mg daily.

Prior to RFM initiation, patients had taken a median of 6 other antiepileptic medications (range 2–13). Additional prior therapies included the ketogenic diet in 54 (41%), the vagus nerve stimulator in 41 (31%), corpus callosotomy in 11 (8%), and focal surgical resection in 9 (7%). Polypharmacy at the time of RFM initiation was common – the median number of concomitant AEDs was 2 (range 0–4). Four patients were taking no other AED at the time RFM was started, 17 (13%) patients were taking 1 other AED, 37 (27%) were on 2 other AEDs, 43 (32%) were on 3 other AEDs, and 34 (25%) were on more than 3 other AEDs. Eighteen patients were on the ketogenic diet at the time of RFM was added. At RFM initiation, 36 (27%) patients were taking VPA, of which 12 were weaned off of VPA during the observation period. RFM serum levels were not routinely assessed, and serum concentrations of concomitant drugs were not assessed in enough patients to report estimates of change due to RFM.

RFM effectiveness and influencing factors

For all patients, the probability of remaining on RFM without additional therapy (primary outcome measure) was 45% at 12 months and 30% at 24 months (see Fig. 1). RFM failure constituted discontinuation in 57 patients, with 38 of these patients starting a new treatment and 2 patients increasing doses of concurrent AEDs. Initiation of additional treatment without RFM discontinuation occurred in 26 patients. For all patients, the probability of remaining on RFM regardless of additional therapy (secondary outcome) was 58% at 12 months and 49% at 24 months. Five patients (4%) were noted to be seizure free for 6 months or greater.

The primary reason for RFM discontinuation was lack of efficacy ($n = 43$; 32%). Five patients (4%) discontinued RFM for lack of tolerability alone – three experienced gastrointestinal side effects including vomiting and gastritis, one experienced imbalance, and one developed a rash. Lack of both efficacy and tolerability were cited as reasons for discontinuation in 19 (14%). Overall, gastrointestinal side effects and loss of appetite were the most commonly reported side effect, occurring in 29 (21%) patients. Reports of side effect occurrence are summarized in Table 3.

RFM retention rates for both the primary and secondary outcome measures were different in LGS patients compared to all others. Median time to RFM failure (defined as either discontinuing RFM or additional therapy) was 18 months in LGS patients compared to 6 months in all others ($p = 0.006$, log rank test). The probability of remaining on RFM without additional therapy at 12 months was 64% in patients with LGS and 40% in those without LGS, and 24 months was 35% in those with LGS and 30% in those without LGS (Fig. 2). For the secondary outcome of discontinuation alone, median time to RFM failure was greater than 27 months in LGS patients compared to 10 months in all others ($p = 0.003$, log rank test). For the group with LGS, the probability of remaining on RFM was 78% at 12 months and 68% at 24 months, compared to 49% at 12 months and 41% at 24 months in the group without LGS (Fig. 3). The unadjusted Cox proportional HR for the primary outcome was 0.51 (95% CI 0.31–0.83, $p = 0.007$), and for the secondary outcome was 0.38 (95% CI 0.20–0.73, $p = 0.004$).

The factors fast or slow drug titration, highest dose (mg/kg/day) and concomitant therapy with VPA were not independent predictors of time to RFM failure, and did not substantially affect the association between LGS diagnosis and RFM failure. The presence of tonic or atonic seizures was possibly associated with longer time to RFM failure but the effect was not statistically significant (unadjusted HR 0.65, 95% CI 0.42–1.01, $p = 0.06$), and did not substantially affect the association between LGS diagnosis and RFM retention rate (adjusted HR 0.55, 95% CI 0.33–0.94). The number of prior AEDs had no effect on time to RFM failure, when comparing patients exposed to 3–5 prior AEDs, or 6 or greater prior AEDs, to those with 2 or fewer prior AEDs (HR 1.03 for each increase in category, 95% CI 0.75–1.4, $p = 0.83$).

Older age at the time of starting RFM was a predictor of greater RFM retention – for each 1 year increase in age at the time of starting RFM, there was a 4% increase in RFM retention rate (unadjusted HR 0.96, 95% CI 0.92–0.99, $p = 0.03$). However the effect was not linear across the whole age spectrum. When evaluated by category (ages 0 to <5 years, 5–9 years, 10–14 years, and 15 years and greater), patients in the 10–14 year age group were more than twice as likely to continue RFM without additional medication than those in the youngest age group (LGS adjusted HR 0.40, 95% CI 0.2–0.8, $p = 0.01$). Patients in the oldest age group, ages 15 years and older, were also more likely to have success with RFM, but the effect was smaller than in the 10–14 age group (LGS adjusted HR 0.54, 95% CI 0.30–0.98, $p = 0.04$). Age was not a confounder of the association between an LGS diagnosis and time to RFM failure (adjusted HR 0.51, 95% CI 0.31–0.84).

In a final model adjusted for age and for number of prior AEDs, time to RFM treatment failure remained longer in those with an LGS diagnosis compared to all others (HR 0.52, 95% CI 0.32–0.86, $p = 0.01$).

Discussion

The key observation of this study is that nearly half of children with refractory epilepsy who are treated with RFM will continue to take the medication for a year or more without additional therapy. The key factors predicting longer duration of RFM treatment with or

without additional therapy were a diagnosis of LGS (compared to those with other epilepsy syndromes), and age over 10 years when starting RFM.

Efficacy in epilepsy drug trials and observational studies is often measured by percent seizure reduction or the 50% responder rate – the proportion of patients who have at least a 50% drop in seizure frequency. Both outcome measures have some disadvantages, particularly when used outside the context of a randomized controlled trial. First, these measures assess efficacy only, and may not reflect real-world usefulness of the drug which may extend beyond effects on seizure number (Sander, 2005). Second, it is unclear how important a 50% drop in seizure frequency is to patients with refractory epilepsy, or how well this outcome impacts quality of life (Ben-Menachem et al., 2010). In fact, the correlation between AED side effects and quality of life scores appears stronger than the impact of seizure control on quality of life (Boylan et al., 2004; Gilliam, 2002; Gilliam et al., 2004). Third, both methods are best used when there is prospective counting of seizure frequency, including a pre-treatment baseline. Used in retrospective studies, these measures are subject to recall bias and to imprecision when recorded in clinic visit notes for clinical, not research purposes.

Retention rate, an outcome measure recommended by the International League Against Epilepsy (ILAE, 1998), is based on measuring treatment persistence at specific time points, or across a span of time. Because it is a composite outcome which reflects effectiveness (efficacy and tolerability), its relevance to clinical practice is much clearer than seizure count based measures. In addition, it has the advantage of not requiring a prospective baseline seizure count and can be used in retrospective studies (Ben-Menachem et al., 2010; Mohanraj and Brodie, 2003). Retention rate has been measured in one of two ways—either as the percentage of a cohort still taking a medication at a specified time point after drug initiation (Chung et al., 2007), or as time to medication failure (defined as discontinuation or addition of another drug) (Marson et al., 2007; Novy et al., 2013; Rosenfeld et al., 2014). The advantages of the latter, particularly in retrospective studies, are that effectiveness can be continuously assessed over a follow up period, without the need for picking an arbitrary follow up point, and the rate of drop out can be estimated. To our knowledge, this is the only study of post-marketing RFM study which has estimated retention rate using survival analysis methods, instead of reporting percentage remaining on the drug at last observation, a time point which is often highly variable (Thome-Souza et al., 2014; Vendrame et al., 2010).

Limitations common to several previously published post-marketing observational studies of RFM in refractory epilepsy include short follow up times, variable or unspecified time points for efficacy assessment, small sample sizes, populations restricted to one epilepsy type, and the retrospective use of the 50% responder rate outcome measure (Dahlin and Ohman, 2012; Joseph et al., 2011; Kim et al., 2013, 2012; Kluger et al., 2009; Mueller et al., 2011; Olson et al., 2011; Thome-Souza et al., 2014; Vendrame et al., 2010). Particularly in studies reporting efficacy at short assessment times, “honeymoon periods” may not be distinguishable from sustained efficacy, which limits the impact of those studies on clinical decision making. To our knowledge, this study has the longest median follow time of post-marketing studies of RFM in patients with mixed epilepsy diagnoses.

In our study, the estimated likelihood of remaining on RFM at 1 year without the addition of further therapy was nearly 50%, indicating greater preference for remaining on the medication than predicted by the 2008 randomized double blind placebo controlled trial in which the 50% responder rate at 3 months was 31.1% in patients with LGS. In a European cohort of 60 patients with childhood-onset refractory epilepsy, retention rates (measured as the percentage of patients still taking RFM at 18 months) were similarly higher (41.7%) than the reported 50% responder rate (26.7%), suggesting that 50% responder rate may underestimate the value of the treatment to the patient (Kluger et al., 2010b). While some may argue that AED retention rate, particularly in treatment resistant patients on polypharmacy, is an only an indirect measure of how well the drug is working, our findings can be translated into a straightforward message for clinicians: *in a broad population of children with refractory epilepsy, the perceived benefit-to-side effect balance for RFM, measured by retention rate which reflects both efficacy and tolerability, is favorable enough that around half will continue taking the medication for at least a year without need for additional therapy.*

Our findings show that the retention rate of RFM in patients with LGS is greater than in patients with other epilepsy types, with a 65% likelihood of remaining on RFM at one year without additional therapy. In animal models of epilepsy, RFM has a broad spectrum of anticonvulsant activity (White et al., 2008), and early pre-approval studies of RFM were not limited to patients with LGS (Palhagen et al., 2001). Regulatory approval for RFM may have been sought first for LGS because an indication for a rare disorder allowed orphan drug status, but limited data from other post-marketing studies have suggested a higher response rates in LGS patients than in other epilepsy syndromes (Kluger et al., 2010b; Thome-Souza et al., 2014). Because little is known about the underlying mechanisms which lead patients with a variety of epilepsy etiologies to the electroclinical syndrome of LGS, it is hard to surmise why RFM may be particularly effective in this population. In the major phase 3 randomized controlled trial of RFM in LGS patients (Glauser et al., 2008), the decline in frequency of tonic and atonic seizures, hallmark seizure types in LGS, was even more robust than decline of total seizure frequency, a possible reason that RFM retention rate was greater in LGS than in other patients in the present study. Our results did not show a statistically significant difference in the effect of atonic or tonic seizures on RFM success, though the study may have been underpowered to evaluate the non-significant effect that was observed. Evidence for RFM usefulness in other generalized epilepsy syndromes compared to epilepsies with focal onset seizures is mixed, with highly variable reports of efficacy in focal epilepsies (Coppola et al., 2014; Grosso et al., 2014; Kluger et al., 2010a; Vendrame et al., 2010).

In our study, an effect of age was noted, with a two-fold greater RFM success rate in patients older than the median age of 10 years compared to younger patients – with a particularly robust effect of age in patients in the 10–14 year category. This effect of age has not been reported in previous studies, though it is unclear whether age was examined as a factor contributing to response. Explanations for this observation are not readily apparent but are perhaps worth examining in other cohorts.

None of the other factors that were chosen a priori for analysis of their effects on retention rate were found to have statistically significant associations. These included the concomitant use of VPA, which is known to decrease the clearance of RFM up to 70%, with marked increases in plasma RFM levels. RFM serum levels were not routinely monitored in this population, so it is unclear whether serum level differed based on concomitant use of VPA in this cohort, where highest daily RFM dose did not significantly differ.

As in other studies, the tolerability of RFM appeared to be high, with very few patients discontinuing the medication for side effects alone. Gastrointestinal side effects, including loss of appetite, were most commonly reported. Because of the small number of patients who were reported to discontinue RFM for tolerability reasons alone, analysis of competing risks was not informative (Williamson et al., 2007).

Though this study is subject to the limitations of retrospective studies, chiefly the dependence on clinical records, it was designed to avoid several of the limitations common in retrospective AED efficacy investigations, particularly concerns around seizure count data, recall bias, and variability in observation time. RFM dosing in this study was variable, with a few patients receiving very low doses. In contrast to RCTs or long term open label extensions of RCTs, the variability in dosing reported here reflects real world practice where patients who fall outside typical weight parameters for age, or patients with a history of perceived sensitivity to medication are given lower milligram per kilogram doses than recommended. Therefore, the observed variation in dosing may not be a limitation but may make these results more applicable to practice. Other observational studies of RFM report similar dosing ranges (Kluger et al., 2010b; Vendrame et al., 2010). An additional limitation is that side effects may have been under-reported due to lack of standardized reporting in clinical practice – a shortcoming that does not affect the primary analysis.

Length-bias is a possible limitation we considered, because of the possibility that patients with LGS were treated with RFM earlier and thus perhaps longer than those without LGS. Though the median length of follow up was slightly longer for LGS patients than for non-LGS patients, the distribution of start times for LGS and non-LGS patients were not different (see Table 1), arguing against a substantial bias in the length of observation between the two groups. Moreover, the difference in hazards is apparent early and remains proportional during the length of observation.

A possible criticism of retention rate as an outcome measure in refractory epilepsy is that treatment inertia may occur when subsequent treatment options are limited – that is, perhaps patients stayed on RFM because no other good treatment options were available at the time. No feasible methods exist for retrospectively assessing number of remaining treatments available for each patient – therefore we were not able to adjust for confounding by this factor. However, we did evaluate the potential effect of the number of AEDs tried prior to RFM on time to RFM failure, and found no relationship – that is, those with many prior antiepileptic treatments had the same risk of RFM failure as those with fewer prior treatments. In addition, the number of prior antiepileptic treatments did not confound the association between RFM retention rate and LGS diagnosis. Even when adjusting for number of prior AEDs, the likelihood of RFM success was still twice as high in those with

LGS compared to those without LGS. In general, it seems prudent to consider studies of medication effectiveness in refractory epilepsy using retention rate in the context of available treatment options during the time period studied.

A final criticism is that drug retention rates may be affected by differences in goals of therapy between groups of patients. We are not able to measure goals of therapy retrospectively, but retention rate incorporates goals of therapy, whether explicitly decided prior to drug initiation or not – that is, if the goal of therapy is met, it is likely that the drug will be continued and no additional therapy will be started. Therefore, retention rate is a useful outcome measure for measuring drug effectiveness across different populations where explicit goals of therapy (whether it is seizure freedom, or 50% reduction in seizures, or a more subjective meaningful reduction in seizures) may differ.

Our study contributes to the growing body of information supporting the use of RFM in pediatric patients with epilepsy resistant to first line medications, particularly those with LGS. We have also demonstrated the application of AED retention rate using survival analysis techniques as a useful outcome measure in retrospective observational studies of refractory epilepsy.

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Figure 1. Kaplan Meier survival estimates for probability of continuing RFM without additional therapy, in months, with point wise 95% confidence bands. Hash marks indicate individuals censored.

Figure 2. Kaplan Meier survival estimates for probability of continuing RFM without additional therapy, by LGS diagnosis, with point wise 95% confidence bands. Hash marks indicate individuals censored.

Figure 3. Kaplan Meier curves for probability of continuing RFM regardless of additional therapy, by LGS diagnosis.

Table 1

Baseline Demographic and Clinical Characteristics of Cohort.

	Total (<i>n</i> = 133)	LGS (<i>n</i> = 39)	Not LGS (<i>n</i> = 94)	<i>p</i>
Sex (M/F)	72/61	17/22	55/39	0.25
Hispanic ethnicity (<i>n</i> , percent)	7 (5)	1 (2)	6 (6)	0.67
Race (<i>n</i> , percent)				
White	96 (75)	26 (68)	70 (78)	0.27
Black	15 (12)	6 (16)	9 (10)	
Asian	10 (8)	5 (13)	5 (5)	
Other or Unknown	7 (5)	1 (3)	6 (7)	
Age at seizure onset (years; median, range)	1 (<1–13)	0.5 (<1–7)	1.5 (<1–13)	0.02
Age at RFM initiation (years; median, range)	10 (0.9–25.7)	11.3 (2.1–23.5)	10 (0.9–25.7)	0.53
Duration of follow up (months; median, range)	20 (1–30)	23 (9–30)	19 (1–27)	0.01
Start time of RFM				0.12
January–June 2009	64 (48)	25 (64)	39 (41)	
July–December 2009	30 (23)	7 (18)	23 (24)	
January–June 2010	30 (23)	6 (15)	24 (26)	
July–December 2010	9 (7)	1 (3)	8 (9)	
Mode of onset				
Focal (<i>n</i> , percent)	31 (23)	–	31 (32)	–
Generalized (<i>n</i> , percent)	49 (37)	19 (49)	30 (32)	–
Both Focal and Generalized (<i>n</i> , percent)	50 (38)	20 (51)	30 (32)	–
Undetermined (<i>n</i> , percent)	3 (2)	–	3 (3)	–
Number of seizure types (median, range)	2 (1–6)	3 (1–6)	2 (1–4)	0.002
AEDs prior to RFM (median, range)	6 (2–13)	4 (2–13)	7 (2–13)	0.11
Patients with atonic seizures (<i>n</i> , percent)	47 (35)	26 (67)	21 (22)	<0.001
Patients with tonic seizures (<i>n</i> , percent)	40 (30)	20 (51)	20 (21)	<0.001
Fast titration (<i>n</i> , percent)	39 (29)	11 (28)	28 (30)	0.56
Maximum RFM dose (mg/kg/day; median, range)	45 (4–105)	49 (4–84)	44 (6–105)	0.22
Concurrent AEDs at RFM start (median, range)	2 (0–4)	2 (0–4)	2 (0–4)	0.65
Patients on concurrent valproate (<i>n</i> , percent)	36 (27)	8 (21)	28 (30)	0.15
Patients on the ketogenic diet (<i>n</i> , percent)	17 (13)	1 (3)	16 (17)	0.18
Patients with vagus nerve stimulator (<i>n</i> , percent)	41 (31)	15 (38)	26 (27)	0.32

Table 2

Etiologic characteristics of cohort (presented as *n*, %).

<i>Genetic etiologies</i>	
Channelopathies	
SCN1A mutation	2 (1)
Infantile developmental encephalopathies	
CDKL5 mutation	1 (1)
PCDH19 mutation	1 (1)
MECP2 mutation	1 (1)
MECP2 duplication	1 (1)
Chromosomal anomalies	
Trisomy 21	3 (2)
Microdeletions and microduplications	5 (4)
Neurometabolic abnormalities	
Mitochondrial	4 (3)
Cerebral malformations	
Focal cortical dysplasia	12 (9)
Polymicrogyria	4 (3)
Lissencephaly	5 (4)
Band heterotopia	3 (2)
Gray matter heterotopia	1 (1)
Tuberous sclerosis	1 (1)
Aicardi syndrome	2 (1)
Other	12 (9)
<i>Acquired insults</i>	
Cerebrovascular	
Perinatal stroke	5 (4)
Hypoxic ischemic encephalopathy	1 (1)
Traumatic brain injury	1 (1)
Infection	1 (1)
<i>Unknown etiology</i>	68 (51)

Table 3Occurrence of side effects; *n* (%).

Gastrointestinal/loss of appetite	29 (21)
Drowsiness	12 (9)
Behavioral problems, new or exacerbation	6 (4)
Incoordination/Ataxia	6 (4)
Cognitive impairment	3 (2)
Rash	3 (2)
Other	1 (1)