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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 ($p = 0.006$).

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

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