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Adjunctive retigabine in refractory focal epilepsy: Postmarketing experience at four tertiary epilepsy care centers in Germany

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ABSTRACT

Purpose: Retigabine (RTG, ezogabine) is the first potassium channel-opening anticonvulsant drug approved for adjunctive treatment of focal epilepsies. We report on the postmarketing clinical efficacy, adverse events, and retention rates of RTG in adult patients with refractory focal epilepsy.
Methods: Clinical features before and during RTG treatment were retrospectively collected from patients treated at four German epilepsy centers in 2011 and 2012.
Results: A total of 195 patients were included. Daily RTG doses ranged from 100 to 1500 mg. Retigabine reduced seizure frequency or severity for 24.6% and led to seizure-freedom in 2.1% of the patients but had no apparent effect in 43.1% of the patients. Seizure aggravation occurred in 14.9%. The one-, two-, and three-year retention rates amounted to 32.6%, 7.2%, and 5.7%, respectively. Adverse events were reported by 76% of the patients and were mostly CNS-related. Blue discolorations were noted in three long-term responders. Three possible SUDEP cases occurred during the observation period, equalling an incidence rate of about 20 per 1000 patient years.
Conclusions: Our results are similar to other pivotal trials with respect to the long-term, open-label extensions and recent postmarketing studies. Despite the limitations of the retrospective design, our observational study suggests that RTG leads to good seizure control in a small number of patients with treatment-refractory seizures. However, because of the rather high percentage of patients who experienced significant adverse events, we consider RTG as a drug of reserve.

1. Introduction

Up to one-third of patients with epilepsy do not achieve seizure freedom with currently available anticonvulsant drugs. The first potassium channel modulator used in the treatment of epilepsy [1,2,3] was approved by the European Medicines Agency (EMA) in March 2011 under the name retigabine (RTG, Trobalt®) and by the United States Food and Drug Administration (FDA) in June 2011 under the name ezogabine (EZG, Potiga®) for use as adjunctive therapy for focal seizures in adult patients. After price negotiations between the German statutory health insurance fund and the manufacturer GlaxoSmithKline® failed due to a negative pricing prospect, RTG was withdrawn from the German market in June 2012 [4] but could still be imported from other European countries for those patients who had obtained good seizure control. The three pivotal, randomized, controlled clinical trials that led to the approval of RTG and one postmarketing, open-label, uncontrolled study included a maintenance period of no longer than 16 weeks [1,2,3,5]. Two long-term, open-label extension studies and a compassionate use program provided long-term results in some of the patients [6,7]. In addition to these controlled studies and programs, long-term postmarketing observations can provide further important insight concerning efficacy and tolerability under "real life conditions" [8,9]. Here, we retrospectively analyzed the clinical experience in patients treated with adjunctive RTG over a period of 4 years at four tertiary epilepsy centers in Germany.

2. Patients & methods

We retrospectively collected data from in- and outpatients with drug-refractory seizures with focal epilepsy syndromes who began RTG treatment after its approval and introduction to the European market in May 2011. The data from each of the participating centers were collected separately and later anonymized and pooled. We excluded patients for whom no follow-up data were available. Patients who had previously participated in premarketing studies of RTG were excluded as well, since we chose to focus on use in a postmarketing environment.

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After RTG was withdrawn from the German market in June 2012, patients who did not return for regular visits were called and informed of this decision. Advice was offered on how to either continue taking the drug or how to schedule visits for therapeutic reevaluation, if so desired by the patient. Data on concurrent anticonvulsants, seizure frequency, initiation and termination of treatment, and adverse events from electronic patient records and/or follow-up phone calls were extracted. In cases where precise reports of seizure frequencies or duration of treatment were lacking, estimates were used.

For example, we used the first day of the month for treatment initiation or termination when no exact date was available.

Numerical seizure frequencies were used when provided. For those cases in which no exact numeric frequencies were provided, estimates were used (n = 69). For example, if a patient record read "(…) had five seizures since the initiation of treatment 5 months ago (…)", a seizure frequency of one per month was assumed. We divided the patients into six groups in an ordinal scale for further analyses. The six outcome groups consisted of (I) seizure-free; (II) response with 50–99% reduction in seizure frequency; (III) partial response with 25–50% reduction in seizure frequency or no change in seizure frequency but a cessation of severe and debilitating seizure types such as generalized tonic–clonic seizures and recurrent status epilepticus; (IV) indifferent response with a change of ±25% in seizure frequency; (V) aggravation with an increase of >25% in seizure frequency or first onset of status epilepticus; and (VI) unclear response. This system enabled us to include patients in whom no exact numbers were documented, e.g. when a progress note read "(…) had no more grand mal seizures (…)", a partial response was assumed or if it read "(…) used to have seizures every week, since starting RTG only had seizures every couple of months (…)", a response was assumed. Patients for whom no follow-up data in seizure frequency existed were excluded from analyses of seizure outcomes. Adverse events were divided into several classes as depicted below. Descriptive and analytic statistics (normality tests, nonparametric, unpaired t-tests, contingency tables, Kaplan–Meier analysis, Cox regression analysis) were calculated using IBM® SPSS® Statistis Version 22 (IBM Corporation, USA) and Graphpad Prism® (Graphpad Software, La Jolla, California, USA). Paired samples were analyzed with Wilcoxon tests. The study was presented to the local ethics committee. Due to the entirely retrospective nature of the study, a full, formal audit was waived.

3. Results

3.1. Patient characteristics

We identified 199 patients from four epilepsy centers. One patient, who was treated at two centers, was excluded. Three patients who were without sufficient follow-up data were excluded as well, leaving 195 remaining patients for analysis. The follow-up period lasted up to 4 years. Daily doses of RTG ranged from 100 to 1500 mg. The patients were started on RTG between May 2011 and June 2012. A summary of patient demographics is provided in Table 1.

Table 1
Summary of patient demographics (AED = antiepileptic drugs, RTG = retigabine).

	n	%
Sex:		
• Male	115	59
• Female	80	41
Epilepsy syndrome:		
• Focal	151	77.4
• Unclassified	44	22.6
Invasive therapy:		
• Resection/vagus nerve/deep brain stimulation	77	39.5
Age, duration, comedication (range):	Mean ± SD	Median
• Current age (12–72)	37.6 ± 13.3 years	35 years
• Age at diagnosis (0–70)	14.2 ± 12.9 years	12 years
• Duration of epilepsy (1–68)	23 ± 12.8 years	22 years
• Number of previous AEDs (2–23)	8.2 ± 4.01	8
• Number of AEDs combined with RTG (1–4)	2.3 ± 0.8	2
• RTG dosage (100–1500 mg)	701.8 ± 283.5	600 mg

3.2. Seizure outcome

Eighty-four patients (43.1%) experienced no apparent effect on seizure frequency. In twenty-nine patients (14.9%), seizure frequency increased during the time period with adjunctive RTG treatment. Nineteen patients (9.7%) showed a partial response with a 25–50% reduction in seizures or freedom from severe seizure events such as status epilepticus or secondary generalized tonic–clonic seizures. Twenty-nine patients (14.9%) responded with a reduction in seizure frequency by more than 50%, and four patients (2.1%) achieved seizure freedom. The mean monthly seizure rate was significantly decreased from 45.6 ± 158.4 [median: 12; min: 0.16; max: 1800] before the initiation of therapy to 34.9 ± 97.3 [median: 10; min: 0; max: 1000] during treatment with RTG (p = 0.002). For those 30 patients (15.4%) who had mostly discontinued RTG in the early titration phase or were early dropouts to follow-up, no quantifiable data on seizure frequency could be retrieved from the patient records. These patients were excluded from the abovementioned analyses on seizure frequencies.

3.3. Retention rate

For our study, 193 patients were available for retention analysis; 22 patients were censored. Median retention lasted 229 days. The one-year retention rate amounted to 32.6%, the two-year retention rate was 7.2%, and the three-year retention rate was 5.73% (Fig. 1).

According to a Cox regression analysis, the following factors were associated with longer retention:

- Favorable seizure outcome (overall p = 0.011; partial response p<0.037, OR = 0.44; 95% CI = 0.2, 0.95; response p = 0.003, OR = 0.43, 95% CI = 0.25, 0.74, seizure freedom p = 0.091, OR = 0.28, 95% CI = 0.66, 1.22).

The following factors were associated with shorter retention:

- Occurrence of adverse events (p = 0.008 OR = 1.96, 95% CI = 1.19, 3.24).
- Initiation of treatment 1–7 months (n = 39) prior to withdrawal from

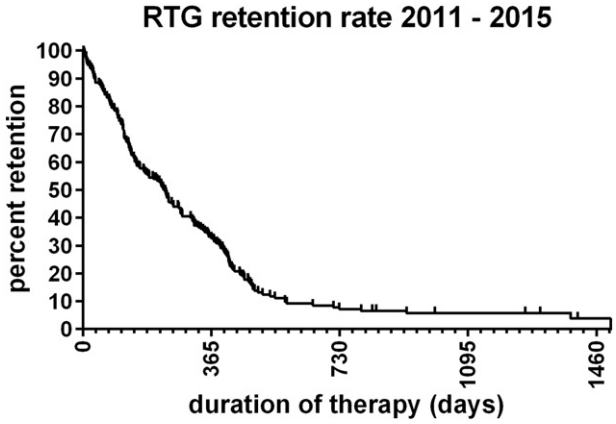

Fig. 1. Retention of RTG shown as a Kaplan–Meier plot (RTG = retigabine).