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Long term retention of retigabine in a cohort of people with drug resistant epilepsy

Tim Wehner [a,b,*], Suganthi Chinnasami [a], Jan Novy [a,b,c], Gail S. Bell [a,b], John S. Duncan [a,b], Josemir W. Sander [a,b,d]

[a] NIHR University College London Hospitals Biomedical Research Centre, National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, United Kingdom
[b] Epilepsy Society, Chalfont St Peter SL9 0RJ, United Kingdom
[c] Department of Clinical Neurosciences, Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne, CH-1011 Lausanne, Switzerland
[d] Stichting Epilepsie Instellingen Nederland (SEIN), Achterweg 5, 2103 SW Heemstede, Netherlands

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ABSTRACT

Purpose: To assess the utility of retigabine (RTG) for epilepsy in clinical practice at a single UK tertiary centre.
Methods: We identified all individuals who were offered RTG from April 2011 to May 2013. We collected demographics, seizure types, previous and current antiepileptic drugs (AEDs), starting and maximum attained daily dose of RTG, clinical benefits, side effects, and reason to discontinue RTG from in- and outpatient encounters until February 28, 2014.
Results: 145 people who had failed a median of 11 AEDs took at least one dose of RTG. One year retention was 32% and decreased following the safety alert by the US Federal Drug Administration (FDA) in April 2013. None became seizure free. 34 people (24%) reported a benefit that was ongoing at last assessment in five (3%). The most relevant benefit was the significant reduction or cessation of drop attacks or seizure-related falls in four women, this persisted at last assessment in two. The presence of simple partial seizures was associated with longer retention, as was a higher attained dose of RTG. Adverse effects were seen in 74% and largely CNS-related or nonspecific and affected the genitourinary system in 13%.
Conclusion: Retention of RTG was less favourable compared to data from open label extension studies of the regulatory trials. In comparison with historical data on similar retention audits retention of RTG at one year appears to be less than lamotrigine, topiramate, levetiracetam, pregabalin, zonisamide, and lacosamide, and slightly higher than gabapentin.

1. Introduction

Retigabine (RTG) is a first-in-class AED that reduces neuronal excitability by enhancing neuronal potassium channel activity. It was licensed in the EU and became available in the UK in 2011. Its efficacy as an add-on medication in people with focal epilepsy was shown in three regulatory randomised controlled trials that assessed daily doses of 600, 900 and 1200 mg, lasting up to 18 weeks.[1–3]

Results of regulatory trials do not necessarily translate well into clinical practice. Many people with pharmacoresistant epilepsy may not meet inclusion criteria for a trial, and a follow-up period of 18 weeks does not inform about efficacy and tolerability in a clinically more relevant longer time frame. At our centre, we have assessed the retention, efficacy and tolerability of novel AEDs over the past 15 years in large cohorts of people with pharmacoresistant epilepsy.[4–8] In April 2013, the FDA issued a safety warning about RTG following reports about retinal pigmentation and blue discoloration of skin and nails in people exposed to the medication in open label extension studies.[9]

We present retention data for RTG from our centre before and after the FDA warning.

Abbreviations: AED, antiepileptic drug; FDA, Federal Drug Administration of the US; GBT, gabapentin; LCM, lacosamide; LTG, lamotrigine; LEV, levetiracetam; PGB, pregabalin; RTG, retigabine; SUDE, sudden unexplained death in epilepsy; TPM, topiramate; ZNS, zonisamide.

* Corresponding author at: National Hospital for Neurology and Neurosurgery, Box 141, 23 Queen Square, London WC1N 3BG, United Kingdom.
Tel.: +44 20 3448 3287.
E-mail addresses: tim.wehner@uclh.nhs.uk, m.wehner@uclh.nhs.uk (T. Wehner), dr.chinnasami.suganthi@gmail.com (S. Chinnasami), jan.novy@chuv.ch (J. Novy), gail.bell@ucl.ac.uk (G.S. Bell), j.duncan@ucl.ac.uk (J.S. Duncan), l.sander@ucl.ac.uk (J.W. Sander).

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2. People and methods

All people advised to start taking RTG between April 2011 and May 2013, at the specialised epilepsy clinics of University College London Hospitals, were identified through pharmacy records and notes review. Exclusion criteria comprised RTG started for reasons other than epilepsy, people who did not start it and, to avoid survival bias, people who had RTG started elsewhere and those who had taken part in a clinical trial of RTG. All but one participant (who had failed and subsequently discontinued six AEDs) started RTG as add-on treatment.

People were followed from the day that RTG was initiated. Data on starting dose, highest exposed daily dose, efficacy and side effects were collected from computerised and paper records of outpatient visits and hospital admissions. We recorded age at starting RTG, age at seizure onset, current seizure types (ILAE classification), history of learning disability, psychiatric comorbidity, and current and previous AED use. At each subsequent clinic visit or telephone encounter, efficacy was assessed as seizure freedom, at least 50% improvement, marked improvement, no change, or worsening of seizures. Side effects were recorded and categorised according to body system affected. The reason for stopping RTG was captured. The study was approved as an audit by the hospital's research ethics committee.

Statistical analysis was performed using Stata v13. The retention rate of RTG was estimated using Kaplan–Meier survival analysis, and effects of different factors were examined using Cox regression analysis.

3. Results

The first person was enrolled in April 2011, and the last one in May 2013. The database was locked at the end of February 2014.

We identified 158 people who had been offered RTG (i.e. a prescription was issued or they were started as inpatients). For 13 of these, there was no evidence in subsequent records that they ever started the medication. We systematically audited all outpatients seen in our clinics over a two-week period in March 2012 ($n = 330$) to assess the efficacy of our enrolment strategy. All nine people who were flagged as starting on RTG were identified, suggesting that we missed very few, if any, people exposed to the medication.

The analysis thus includes 145 people followed for 0–2.6 years (mean 0.75 years, median 0.60 years); one stopped the drug on the day it was started. Demographic data are summarised in the table (Table 1).

As of February 28, 2014, six people (4%) were still on RTG. Three people (2%) had been lost to follow-up and two had died (one from SUDEP, one cause unknown; all while still on RTG).

Using survival analysis, estimated retention at one year was 30% (95% CI 22.6, 37.7%, Fig. 1). Altogether 11 people were continuing with RTG at last follow-up although two of these had been advised to withdraw it due to the FDA alert. Of the 134 who stopped, 82 (61%) did so prior to 26th April 2013 (date of FDA alert).[9] One person started RTG after the FDA warning.

One person with daily seizures at baseline became seizure free for three weeks. Thirty-four people (23%) had a period of 50% reduction in seizure frequency or of patient-reported 'marked improvement'. Of 26 people with marked improvement, three (9%) had marked improvement (nine to 27 months) at last follow-up. Twenty-three people had a period of transient marked improvement for between one and 28 months (mean 8.8 months, median six months). Of nine people with a 50% reduction in seizure frequency, two still had a 50% reduction at last follow-up. One of the seven who did not have 50% seizure reduction at last follow-up did; however, still report marked improvement for the previous seven months at last follow-up.

Table 1
Patient demographics.

Demographic data ($n = 145$)	Number	Percentage
Age when starting RTG	42.0 (median)	17–66 (range)
Gender (female)	84	57.9%
Age at epilepsy onset	13 (median)	First year of life–48 (range)
Learning disabilities	28	19.3%
Psychiatric history	54	37.2%
Focal epilepsy	137	94.5%
Symptomatic	83	57.2%
Cryptogenic	54	37.2%
Generalised epilepsy	6	4.1%
Symptomatic	2	1.4%
Cryptogenic	2	1.4%
Idiopathic	2	1.4%
Unclassified	2	1.4%
Number of concomitant AEDs		
None	1	0.7%
One	20	13.8%
Two	54	37.2%
Three	36	24.8%
Four or more	34	23.4%
Number of AEDs previously tried (excluding current AEDs)	9 (median)	1–17 (range)
Tried 6 AEDs or more previously	109	75.2%
RTG starting daily dose		
50 mg	61	42.1%
100 mg	10	6.9%
150 mg	63	43.4%
200 mg or more	11	7.6%
Maximal dose of RTG	450 mg (median)	50–1500 mg (range)
Attained dose of 600 mg or higher	65	44.8%
Disposition		
Continuing at last follow-up	11	7.6%
Stopped	134	92.4%
Stopped because of side effects	55	41.0%
Stopped because of inefficacy/worsening	36	26.9%
Stopped because of side effects & inefficacy/worsening	23	17.2%
Stopped because of FDA alert	20	14.9%

The maximum dose attained was associated with retention, with those who achieved higher doses having longer retention. The presence of simple partial seizures was also associated with retention (HR 0.59, 95% CI 0.42–0.85) compared with those without simple partial seizures. Additionally age at starting RTG (HR 1.02, 95% CI 1.00, 1.04) affected retention.

We found no other demographic or clinical variable to affect RTG retention (survival analysis). Specifically, gender (HR 0.80), age at onset of epilepsy (HR 1.02), having generalised epilepsy (compared with focal onset; HR 1.29), number of past AEDs tried (compared with 1–6 previous AEDs, HR 1.01 for 7 or 8 previous AEDs, 1.04 for 9 or 10 previous AEDs, and 1.08 for 11 or more previous AEDs), number of concomitant AEDs (3 or more compared with 2 or fewer; HR 0.94), starting dose of RTG (>100 mg daily compared with 100 mg daily or less, HR 0.72), or seizure types (with the exception of simple partial seizures) did not affect retention. In multivariable analysis including those variables with $p < 0.2$ in univariable analysis (with the exception of absence seizures, experienced by only five people), the variables "maximum dose attained" and "presence of simple partial seizures" remained significant. Compared with those with a maximum doses of 300 mg or less, the HR was 0.46 (95% CI 0.28, 0.74) for those taking 350–450 mg/day, was 0.44 (95% CI 0.28, 0.71) for those taking 500–600 mg/day, and was 0.21 (95% CI 0.13, 0.37) for those taking at least 700 mg/day. The HR for those with simple partial seizures (compared with those who did not have simple partial seizures) was 0.70 (95% CI 0.49, 0.997). The FDA warning from April

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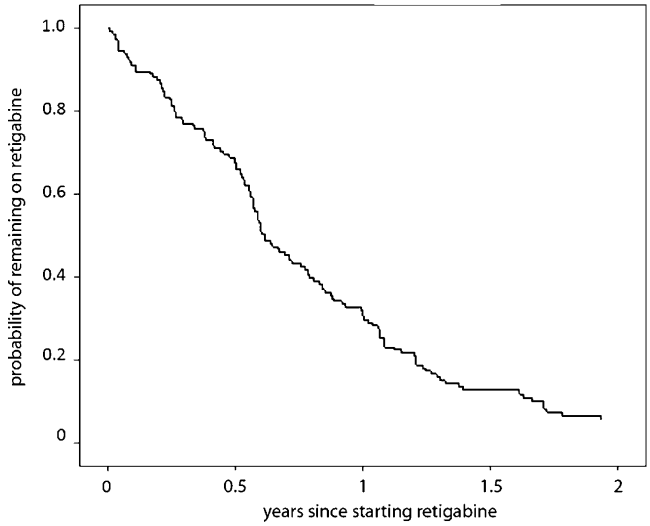

Fig. 1. Retention of RTG as Kaplan–Meier plot.

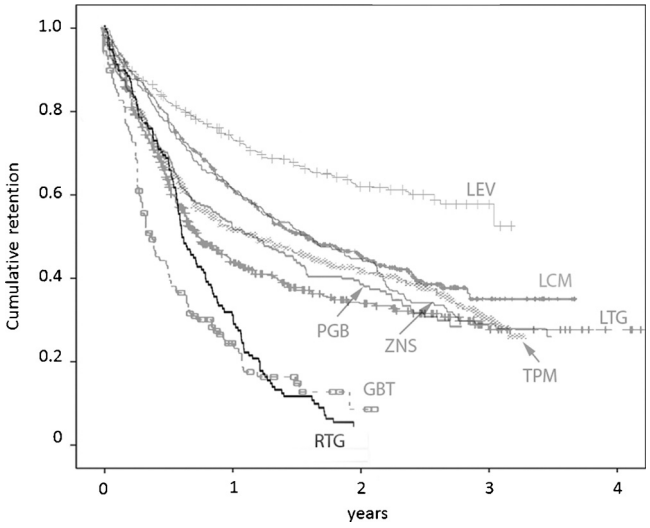

Fig. 2. Retention of RTG compared to historical retention data using similar methods on gabapentin (GBT),[4] lamotrigine (LTG),[4] lacosamide (LTG),[8] levetiracetam (LEV),[5] pregabalin (PGB),[6] topiramate (TPM),[4] and zonisamide (ZNS).[7] Figure in part reproduced from Novy et al., 2013.[8]

2013 was given as the primary reason to stop RTG in 38% of those still on the drug at this point, and there was a significant difference in retention before and after the warning (log rank test $p = 0.0001$). One year retention was 31.9% (95% CI 22.3, 41.8%) before the warning and 8.1% (95% CI 1.4, 22.7%) thereafter.

4. Notable individual benefits

A 35-year-old woman with daily seizures and weekly seizure-related falls reported complete cessation of drop attacks after starting RTG for 32 months at last follow-up. A 19-year-old woman with daily drop attacks at baseline experienced a marked reduction of these for 9 months, when she was lost to follow-up.

Two more women reported transient complete or almost complete cessation of drop attacks for 8 and 9 months, but drop attacks returned at the previous frequency thereafter.

One woman became unintentionally pregnant on RTG (in combination with levetiracetam and lacosamide). She and the foetus are doing well at last follow-up 5 months into the pregnancy.

5. Adverse effects

Adverse effects were experienced by 107 people (74%). Twenty-four (17%) reported increase of their seizure frequency or intensity. Somatic side effects were observed in 100 people (69%) after starting RTG, and 17 people (13%) experienced psychiatric side effects.

The most common side effects reported were attributed to the CNS (cognitive slowing, double vision, speech disturbance etc., $n = 55$, 38%) or nonspecific (fatigue, weight gain; $n = 54$, 37%). Problems with urination (urinary retention, dysuria, or incontinence) were seen in 13 people (9%), a new skin rash in five (3%), lip discoloration in one, and gastrointestinal problems in five (3%).

6. Discussion

Retention at one year was less favourable in this cohort (30%) compared with data from both the open label extension studies of two licensing studies (60%),[10] and historical data from our centre on retention of lamotrigine (46%),[4] topiramate (52%),[4] levetiracetam (75%),[5] pregabalin (52%),[6] zonisamide (62%),[7] and lacosamide (62%),[8] and slightly better than gabapentin (23%, Fig. 2).[4] Nobody on RTG in this assessment achieved seizure freedom for at least six months, compared to 13% in the open label extension studies,[10] and transient or terminal six month seizure freedom rates of 2 (lamotrigine)–11% (levetiracetam) in our previous retention audits mentioned.[4–8] Differences in the study populations may explain why retention and 50% responder rate were lower in this cohort than in the regulatory trials and their open label extension studies.[10,11] People could participate in the regulatory trials if they had ongoing seizures despite being on one to three AEDs.[1–3] People in the current cohort had failed a median of nine AEDs (excluding current AEDs) and can thus be considered highly pharmacoresistant. Nearly half of the people (48%) took RTG in addition to three or more AEDs, compared to 24–31% in the RTG treatment arms in the regulatory trials.[1–3] This may explain the relatively low median dose of RTG (450 mg) achieved by people in this cohort, and, in turn, the much lower 50% responder rates compared to the regulatory trials and open label extension studies.[1–3,10,11] In fact, only 45% of people reached a dose of 600 mg or above, which has been postulated the minimum effective dose in the regulatory trials.[1–3,11]

People who attained higher doses had longer retention. This may be that those who attained higher doses had better efficacy and therefore continued to take RTG longer; alternatively that those who tolerated RTG sufficiently well to continue to take it therefore reached higher doses. It is unclear why people with simple partial seizures had longer retention than those without. In our previous assessments, we did not find any correlation (positive or negative) of retention rates and seizure types.

The clinically most relevant benefit observed in this cohort was cessation or marked reduction in drop attacks or seizure-related falls in four people. To the best of our knowledge, this has not been reported before. Falls are not specific for a particular seizure type,[12] and no current video EEG data were available to assess the mechanism of seizure-related falls in these people. Therefore, it remains unclear whether RTG affects a particular seizure type leading to falls.

Adverse effects were broadly similar to those in regulatory trials and their open label extension studies, in that they were either nonspecific or linked to the CNS. Genitourinary side effects (urinary retention, urinary incontinence, or dysuria) were reported by 9% of people in this cohort compared with 12% in the open label extension studies.[10]

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The limitations of our approach also affect the reason for discontinuation. While our best efforts were made to capture the reason for discontinuation, in clinical reality the decision to discontinue an AED is most often likely due to a combination of lack of efficacy and actual or potential adverse effects. It is thus not surprising that the FDA warning in April 2013 affected retention.

7. Conclusion

The presumed mechanism of action of RTG, reduction of neuronal excitability through opening of potassium channels did not translate into sustained benefit in the majority of people with highly refractory epilepsy in this cohort. Even prior to the FDA warning, retention was unfavourable compared to historical controls on lamotrigine, topiramate, levetiracetam, pregabalin, zonisamide, and lacosamide. Nonetheless, our data suggest a potential benefit in some people with drop attacks or frequent seizure-related falls. Further research is suggested to investigate this effect.

Conflict of interest

UCL and Epilepsy Society have received fundings from Glaxo Smith Kline (GSK), the license holder of RTG. GSK played no part in this assessment. GSB's husband is employed by, and has shares in, GSK.

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