Journal of Central Nervous System Disease

REVIEW

Efficacy of Retigabine in Adjunctive Treatment of Partial Onset Seizures in Adults

Michele Y. Splinter

University of Oklahoma Health Sciences Center, College of Pharmacy, Department of Pharmacy: Clinical and Administrative Sciences, Oklahoma City, OK. Corresponding author email: michele-splinter@ouhsc.edu

Abstract

Objective: To evaluate efficacy and tolerability of retigabine (ezogabine, US adopted name) in the adjunctive treatment of partial-onset seizures in adults. Retigabine is the first anticonvulsant in its class, decreasing neuronal excitability by opening voltage-gated potassium channels.

Methods: MEDLINE and EMBASE were systematically searched using search terms retigabine and ezogabine for randomized controlled trials published from 1980 through August 17, 2013. Additionally, articles relating to pharmacology, pharmacokinetics, tolerability and interactions were examined for inclusion. Published abstracts and websites of the Food and Drug Administration and European Medication Agency were reviewed for additional relevant information.

Results: One phase IIb and two phase III trials were identified. Retigabine has been reported to have dose dependent efficacy in adjunctive treatment of resistant partial-onset seizures in adults in doses of 600, 900 and 1200 mg/day. Similar to other anticonvulsants, the most common adverse events were central nervous system related. Retigabine has several unique adverse events compared to other anticonvulsants: urinary retention and, with extended use, pigment changes to the skin and retina. Retigabine is metabolized by glucuronidation and acetylation. There are few drug interactions with retigabine.

Conclusions: Retigabine has been shown to have efficacy when used as adjunctive therapy in partial-onset seizures. It has a novel mechanism of action, activation of voltage-gated potassium channels. It has less drug interactions than many other anticonvulsants because it is not metabolized through the P-450 system. Its place in therapy has yet to be determined, especially with recent reports of pigment discoloration of skin and the retina with extended use.

Keywords: anticonvulsant, antiepileptic drugs, epilepsy, ezogabine, retigabine

Journal of Central Nervous System Disease 2013:5 31–41

doi: 10.4137/JCNSD.S9299

This article is available from http://www.la-press.com.

Introduction

Retigabine (RTG; international non-proprietary name), also known as ezogabine (EZG; US adopted name), was approved as adjunctive treatment in partial seizures in Europe in March 2011 and in June 2011 in the US.[1,2] It is first in its class as a neuronal potassium channel opener with a primary mechanism of action as a positive allosteric modulator of KCNQ2-5 (Kv7.2-7.5) ion channels.[3] Retigabine is a derivative of flupirtine which has been marketed as a non-opioid centrally acting analgesic in Europe and which demonstrated anticonvulsant efficacy in the National Institute of Neurological Disorders and Stroke Anticonvulsant Screening Project in the 1980s.[4] RTG was previously named D-23129 (free base) and D-20443 (HCL salt version).

The incidence of epilepsy was estimated to be 69 million world-wide in 2010 with up to 30% labeled as refractory to medical therapy.[5,6] The International League against Epilepsy recently developed a global consensus definition of drug-resistant epilepsy.[7] It is defined as a failure of adequate trials of two tolerated, appropriately chosen, and appropriately used antiepileptic drug regimens (whether administered as monotherapies or in combination) to achieve sustained freedom from seizures. The randomized controlled phase III trials with RTG were performed before this definition was released, but inclusion criteria met this definition.[8,9] Despite being labeled with drug refractory epilepsy, approximately 5% per year obtain a 6-month terminal seizure remission.[10] Predictors for not obtaining remission include a history of status epilepticus, younger age at intractability, number of failed drug therapies and presence of mental retardation.

Methods

MEDLINE and EMBASE were systematically searched using the search terms retigabine and ezogabine from January 1980 through August 17, 2013. Trials were included for analysis of clinical efficacy and tolerability if they were randomized controlled trials which studied the effects of RTG in partial seizures. Additional articles relating to pharmacology, pharmacokinetic properties, and drug interactions were reviewed for inclusion in the review. Articles were also identified from the reference lists of published articles. Published abstracts and websites of the Food and Drug Administration and European Medication Agency were reviewed for additional relevant information.

Results

A total of 408 citations were identified from the electronic search of MEDLINE and 719 citations from EMBASE. Efficacy and tolerability results were obtained from three randomized trials. Additionally, interim results from two open-label extension trials of the Phase III trials were reviewed.

Mechanism of Action

Other marketed anticonvulsants (AEDs) block voltage-gated sodium or calcium channels, enhance activity of the inhibitory neurotransmitter gamma aminobutyric acid (GABA), block receptors of the excitatory neurotransmitter glutamate, or modulate the synaptic vesicle protein 2A (SV2A).[11] RTG decreases neuronal excitability by acting as an opener of KCNQ channels KCNQ2-5.[4] The potency of RTG at the KCNQ channels based on determinations of the half maximal effective concentration (EC50) has been ranked as KCNQ3 > KCNQ2/3 = KCNQ3/5 > KCNQ2 > KCNQ4 = KCNQ5 (range 0.6–6.4 μM). RTG causes a concentration dependent hyperpolarizing shift of the activation threshold which results in stabilization of the resting membrane potential.[3]

Mutations in the KCNQ family of genes are associated with inherited diseases: KCNQ1 mutations with about half of the hereditary cases of long QT syndrome, KCNQ4 mutations with progressive hearing loss and KCNQ2 or KCNQ3 mutations with benign familial neonatal convulsions.[12–16] RTG does not act on KCNQ1 channels which are cardiac specific.[17] KCNQ2 and KCQNQ3 are primarily found in the nervous system and coassemble in tetramers.[18]

In vitro studies have suggested other anticonvulsant mechanisms of RTG including enhanced inhibitory effects of gamma-aminobutyric acid (GABA).[4] Higher concentrations of RTG are required to produce significant potentiation (≥10 μM) than are required at KCNQ channels or attained in patients with epilepsy.

On a molecular level, using homology models, Wuttke and colleagues' work suggests formation of a hydrophobic pocket between the S5 and S6 segments of Kv7.2 (KCNQ2) channel upon opening of

the channel.[19] This facilitates the docking of the RTG molecule, and consequently, stabilization of the open channel conformation. Their model predicts a lipophilic interaction between the fluorophenyl ring of RTG and the aromatic TRP236 at the cytoplasmic end of S5. In addition, the authors postulated that the slowing of the deactivation time course by RTG was due to RTG binding to the activation gate on S6, Gly301.

Animal Models

RTG has been shown to be effective in a large number of animal models representing a variety of types of seizures.[20] These include kindling models which stimulate the amygdala or hippocampus used to model complex partial and secondary generalized seizures, the lamotrigine-resistant amygdala kindled rat and the 6-Hz psychomotor seizure test to model pharmacoresistant epilepsy, and administration of D,L-homocysteine thiolactone in which a cortical lesion has been generated by cobalt to model status epilepticus.[20–23] RTG was not found to be effective in preventing clonic seizures induced by bicucullin, motor seizures induced by strychnine, or absence seizures following the administration of the $GABA_A$ blocker, pentylenetetrazole, or in the Genetic Absence Epilepsy Rats of Strasbourg model.[20,24] There were conflicting studies on RTG's ability to increase the seizure threshold for myoclonus induced by picrotoxin.

Pharmacokinetics

The pharmacokinetic profile of single and multiple doses of RTG were determined in a randomized, placebo-controlled, inpatient study of 45 healthy male participants aged 21 to 44 years.[25] Single doses of 100, 200, 250 or 300 mg were given on day one and then every twelve hours for an additional 14 days. Additionally, a dose-escalation group received an initial dose of 200 mg and a 100 mg increase every 4 days to a target dose of 700 mg per day. For single doses, the mean times to maximum concentration were 1.5 to1.8 hours. A high fat meal delayed, but did not reduce, absorption. Mean apparent volume of distribution (Vd/F) ranged from 6.2 to 8.8 L/kg and 5.1 to 7.4 L/kg for single and multiple doses, respectively. Mean terminal half-life ($t_{½}$) was 8 hours with an apparent oral clearance (Cl/F) of 0.7 L/h/kg in white participants. Black participants had a higher exposure rate with Cl/F and Vd/F values 25% and 30% lower, respectively, than white participants. Mean trough RTG concentration in the evening was 63% of the trough concentration in the morning, suggesting a circadian rhythm effect.

RTG and its N-acetyl active metabolite (NAMR, also known as ADW 21-360) are 80% and 45% bound to protein and therefore displacement by other medications is not predicted to occur.[26] The volume of distribution is 2–3 L/kg following intravenous dosing. NAMR is less potent than RTG in animal seizure models.

RTG is metabolized by glucuronidation through the uridine diphosphate glucuronyl transferase (UGT) isoenzymes UGT1A4, UGT1A1, UGT1A3 and UGT1A9 and by acetylation.[27–29] Elimination of RTG was quantified in a study of [^{14}C]-RTG in six healthy males.[29] Eighty-four percent of the 200-mg dose was recovered in the urine within 72 hours, 9% in the feces over 96 hours, and an additional 5% in the feces in the following days. RTG was excreted by the kidney as 36% unchanged and as 7 metabolites, including NAMR (18%), two N-glucuronides of the parent drug (16% and 2%) and 2 N-glucuronides of NAMR (4% and 2%).

RTG and NAMR can be quantified in plasma with tandem mass spectrometric detection in the positive-ion atmospheric pressure chemical ionization mode down to 1 ng/mL.[30]

Special populations

Sex

The impact of sex on the pharmacokinetic profile of RTG was investigated in a single-site, single-dose (200-mg), open-labeled study in 12 young women (aged 25–39 years), 12 elderly women (aged 66–81), 12 young men (aged 21–40) and 12 elderly men (aged 67–82).[31] The maximum concentration (C_{max}) and area under the curve (AUC) were 56% and 20% higher in young women than in young men and 103% and 31% higher in elderly women than in elderly men. These differences did not result in significant differences in weight-normalized clearance, which led the authors to conclude these differences were due to higher doses per kilogram of body weight in women compared to men. Because the starting dose was well tolerated by both sexes and is titrated upwards to effective and tolerable doses, no dosing differences are recommended based on sex.

Geriatric

In the above study, pharmacokinetic differences were also compared between the young and elderly participants. Elderly participants had a significantly reduced Cl/F and increased AUC and $t_{½}$ for RTG and NAMR compared to younger participants. The authors attributed this result to lower mean glomerular filtration rates in the elderly participants (a 27% decrease in men and a 40% decrease in women). In patients greater than 65 years, it is recommended to initiate the dose at 50 mg three times a day (TID) vs. 100 mg TID and to lower the maximum dosage to 250 mg TID vs. 400 mg TID.

Renal impairment

Pharmacokinetic parameters were documented following a 100 mg dose of RTG in patients with mild (creatinine clearance [CrCl] 50–80 mL/min), moderate (30–50 mL/min) and severe (<30 mL/min) chronic renal disease, those with end stage renal disease requiring hemodialysis, and in healthy volunteers.[32] Compared to healthy volunteers (n = 6), renal clearance of RTG was decreased by 25%, 50% and 70% in the mild (n = 5), moderate (n = 5), and severe (n = 4) renal disease groups. The mean $t_{½}$ in the dialysis group (n = 6) was 23 hours vs. 8 hours for the healthy volunteers. An initial dose of 50 mg TID and maximum dose of 200 mg TID is recommended for patients with CrCl less than 50 mL/min and those on dialysis.[26]

Liver impairment

The effect of liver disease on Cl/F, renal clearance and AUC was investigated following a 100 mg dose in patients with mild (Child-Pugh score 5–6), moderate (7–9) and severe (>9) hepatic impairment and in healthy volunteers (n = 6 in each cohort).[33] There were no differences in Cl/F between healthy volunteers and those with mild impairment, but it was 30% and 50% lower in groups with moderate and severe impairment, respectively. It is recommended to decrease both initial and maximum dosages in patients with moderate and severe impairment.[26]

Gene mutations

In studies of microsomal preparations from the liver of a patient with Crigler-Najjar type II syndrome and of human kidney microsomes, both lacking UGT1A, one RTG glucuronide was synthesized suggesting other members of the UGT1 and UGT2 gene family may be involved in the metabolism of RTG and that metabolism is not restricted to the liver.[29]

Clinical Efficacy

The efficacy and safety of retigabine as adjunctive therapy for refractory localization-related seizures has been investigated in three randomized, double-blind, placebo-controlled multicenter, parallel-group trials and two open-label extension trials.[8,9,34,35] Porter and colleagues conducted a phase IIb dose-adjustment study.[34] RESTORE (Retigabine Efficacy and Safety Trials for Partial Onset Epilepsy) 1 and 2 were phase III studies which incorporated recommendations from regulatory agencies, the Food and Drug Administration (FDA) in the United States and the European Medicines Agency (EMA) in Europe, for subsequent approval.[8,9] These studies were followed by open-label studies and interim results of the phase III trials have been published.[35] The majority of the patients in the RTG arms were aged 18–64 years (802/813, 98.6%), with only 3 (<1%) younger than 18 years and 8 (<1%) older than 65 years.[36] The majority were Caucasian (89.3%).

Phase II study

In the phase IIb study, retigabine 600, 900 and 1200 mg/day in three equally divided doses every 8 hours, were assessed for safety and efficacy in patients aged 16 to 70 years of age.[34] Even though 537 patients were recruited from 17 centers in Europe, Australia and the United States, only 399 patients were randomized. The primary reason for exclusion from randomization was not meeting the baseline seizure criteria of four partial-onset seizures per month with no 30-day seizure free period while on stable doses of one or two AEDs. Vagus nerve stimulators were allowed, but considered as one AED. The safety population was comprised of 397 patients who received at least one dose of study treatment and the ITT (intention-to-treat) efficacy population consisted of 396 patients who also had seizure data recorded in a daily diary. The study consisted of an 8-week baseline phase, 8-week forced titration phase, and an 8-week maintenance phase. During the titration phase, patients received 100 mg TID during the first week and increases of 150 mg/day at weekly intervals

until the target dose was reached. The dose could be reduced by 100 mg/day at weekly intervals up to two times during weeks 7 and 8 of the titration phase.

Patients were excluded from the study if they had treatable causes of their seizures or a history of non-electrical seizures or status epilepticus within 30 days prior to screening. The use of felbamate, vigabatrin, tiagabine, other non-established AEDs, any drug that might interfere with the metabolism or absorption of AEDs, and medications that would lower seizure threshold were not permitted. Women of childbearing potential could not be pregnant or lactating and had to use a reliable method of contraception.

The median percent change in monthly total partial-seizure frequency during the double-blind phase compared with baseline frequency was the primary efficacy outcome. Secondary outcomes were responder rate, the proportion of patients with ≥50% reduction from baseline in total partial-seizure frequency at the end of the double-blind treatment phase, and the clinical improvement at the end of the double-blind treatment phase vs. baseline utilizing a 7-point clinical global improvement score. There was a dose-dependent effect, with significant differences between 900 and 1200 mg/day arms vs. placebo arm, but not with the 600 mg/day arm. The authors attributed the poor results of this arm to outliers, especially one patient that had an apparent increase of seizure frequency of over 1700%. Results of this study and the phase III studies are presented in Table 1.

Phase III studies

RESTORE 1 which assessed retigabine 1200 mg/day and RESTORE 2 which assessed retigabine 600 and 900 mg/day were phase III trials.[8,9] They were designed similarly to the dose adjustment study with the following differences: eligibility age was raised to 18–75 years, number of stable AEDs was raised to one to three, use of a vagus nerve stimulator was again allowed but did not count as one of the AEDs, and the baseline seizure free period was lowered to 21 days. Fertile males were required, as were

Table 1. Clinical outcomes of randomized, double-blind trials of adjunctive retigabine in partial-onset seizures.

Trials	Median % reduction in 28-day seizure frequency	Responder rate, %*	Seizure freedom, n (%)	Completion rate (%)
A. Intent-to-treat population from baseline to end of double-blind treatment phase (FDA population)				
Porter, et al[34] (n = 396)			Not reported	
Placebo (n = 96)	13.1	15.6		87.5
600 mg/d (n = 99)	23.4 (NS)	23.2 (NS)		82.8
900 mg/d (n = 95)	29.3 ($P = 0.0387$)	31.6 ($P = 0.0214$)		80
1200 mg/d (n = 106)	35.2 ($P = 0.0024$)	33.0 ($P = 0.016$)		70.8
RESTORE 2[8] (n = 538)			Not reported	
Placebo (n = 179)	15.9	17		85.5
600 mg/d (n = 181)	27.9 ($P = 0.007$)	31.5 ($P = 0.002$)		74.6
900 mg/d (n = 178)	39.9 ($P < 0.001$)	39.3 ($P < 0.001$)		67
RESTORE 1[9] (n = 305)				
Placebo (n = 152)	17.5	17.8	n = 0 (0%)	83.6
1200 mg (n = 153)	44.3 ($P < 0.001$)	44.4 ($P < 0.001$)	n = 3 (2%)	63.4
Trials	**Median % reduction in 28-day seizure frequency**	**Responder rate, %***	**Seizure freedom, n (%)**	
B. Intent-to-treat population from baseline to end of maintenance treatment phase (EMA population)				
RESTORE 2[8] (n = 471)				
Placebo (n = 164)	5.1	18.9	2 (1.2)	
600 mg/d (n = 158)	25.0 ($P = 0.002$)	38.6 ($P < 0.001$)	5 (3.2)	
900 mg/d (n = 149)	30.9 ($P < 0.001$)	47.0 ($P < 0.001$)	7 (4.7)	
RESTORE 1[9] (n = 256)				
Placebo (n = 137)	18.9	22.6	Not reported	
1200 mg (n = 119)	54.5 ($P < 0.001$)	55.5 ($P < 0.001$)		

Note: *Percentage of patients with seizure reductions ≥50% from baseline in 28-day total partial-onset seizure frequency.
Abbreviation: RESTORE, Retigabine Efficacy and Safety Trials for Partial Onset Epilepsy.

women of childbearing potential, to use an acceptable method of birth control. Tiagabine as a baseline AED was allowed. Those with creatinine clearance of < 50 mL/minute and QT_c (Bazett) intervals of >430 milliseconds for men and >450 milliseconds for women were excluded from these studies. Recruitment for RESTORE 1 was from North America, Argentina and Brazil between August 2005 and January 2008, whereas recruitment for RESTORE 2 included countries in Europe and South Africa, but not countries in the western hemisphere with the exception of the United States between February 2006 and April 2008. The titration phase was reduced to 4 weeks for RESTORE 2 and 6 weeks for RESTORE 1, but the maintenance period was extended to 12 weeks and there was a four-week transition phase for those enrolling in open-label extension trials. There was a single dose reduction of 150 mg/day for those unable to tolerate the target dose in RESTORE 1 during week 7. Those unable to achieve the target dose or unable to tolerate the single dose reduction discontinued the study. There were no dose reductions permitted in RESTORE 2.

The primary outcomes for RESTORE 1 and 2 varied dependent upon the regulatory agency. The primary outcome for the FDA was the change in total partial seizure frequency per 28 days from baseline to double-blind period for RTG 900 and 1200 mg/day vs. placebo for RESTORE 2 and RESTORE 1, respectively. Whereas the primary outcome for the EMA was the proportion of responders from baseline to maintenance phase with RTG 900 and 1200 mg/day vs. placebo, respectively for RESTORE 2 and RESTORE 1. Those that discontinued the study during the titration phase were not included in the ITT population for the EMA evaluation, but were included in the ITT population for the FDA evaluation. Differences were statistically significant for all primary outcomes in treatment arms compared to placebo arms. Results for both of these studies are summarized in Table 1.

Long-term open label extension (OLE) trials

To evaluate long term safety and tolerability of RTG, patients completing maintenance phases of RESTORE 1 and RESTORE 2 were recruited to participate in OLE trials. Efficacy of long-term RTG was a secondary objective.[35] Participants in study 304 (extension of RESTORE 2) and study 303 (extension of RESTORE 1) underwent a 4-week (study 304) and 6-week (study 303) double-blind transition phase to target doses of 900 mg/day and 1200 mg/day, respectively. Lower doses of 600 mg/day (Study 304) or 900 mg/day (Study 303) were acceptable for the maintenance phase in patients unable to tolerate

Table 2. Adverse events occurring in ≥10% of patients in RESTORE 1 and 2.*[8,9]

Event	RESTORE 2[8]			RESTORE 1[9]	
	Placebo (n = 179)	RTG 600 mg/day (n = 181)	RTG 900 mg/day (n = 178)	Placebo (n = 152)	RTG 1200 mg/day (n = 153)
Central nervous system					
Dizziness	6.7	17.1	26.4	13.8	40.5
Somnolence	10.1	14.4	26.4	17.8	31.4
Fatigue	2.8	17.1	15.2	7.9	15.7
Confusional state	0	1.7	5.1	2.0	14.4
Headache	14.5	11.0	17.4	18.4	12.4
Dysarthria	0	5.0	1.7	2.0	12.4
Ataxia	NR	NR	NR	3.9	11.8
Vision blurred	1.7	0.6	5.1	2.6	11.8
Tremor	2.2	1.7	9.0	3.9	11.1
Gastrointestinal					
Nausea	3.9	6.1	6.7	6.6	10.5
Urinary tract					
Urinary tract infection	NR	NR	NR	8.6	11.8

Note: *Data presented as percentage of patients in safety population.
Abbreviations: RESTORE, Retigabine Efficacy and Safety Trials for Partial Onset Epilepsy; RTG, Retigabine; NR, not reported in RESTORE 2 because <5%.

the target dose during the transition phase. During the maintenance phase, RTG could be used as monotherapy or adjunctive therapy to 1–3 approved AEDs with or without vagus nerve stimulation. Investigators could adjust doses by 150 mg/day each week and use unequal doses or twice-daily dosing within 600–1200 mg/day to optimize efficacy and tolerability. Also, concomitant AEDs could be modified, tapered or discontinued. If RTG was discontinued, a 3-week tapering period was used.

Ninety-two percent of patients who completed RESTORE 2 and 81% who completed RESTORE 1 entered the extension trials. An interim analysis of data to October 2, 2009 included information on 556 patients who received a dose of open-label RTG including 242 (44%) and 314 (56%) who had been in the placebo and treatment arms, respectively. From baseline to data cutoff, a median reduction of 53% (10.4 to 5.1 seizures) was observed in the 28-day total partial-seizure frequency. Responder rate during this time period was 52.5% and increased over time as the number of patients remaining on RTG decreased. Continuous 6-month seizure free rates were 10.6% (n = 46), 13.1% (n = 44), and 19.1% (n = 35) for participants exposed to 6, 12, or 24 months of RTG.

Tolerability

Retigabine's safety profile was reported in the randomized controlled trials and the open-label extension trials.[8,9,34,35] Most ADEs were mild to moderate in severity and occurred during the forced titration period, accounting for the majority of withdrawals. The incidence of new ADEs generally decreased during the maintenance phase. Of the 813 patients in the placebo-controlled trials, 559 (68.8%) completed the study in which they were enrolled.[36] Discontinuance occurred due to an ADE in 181 (22.3%) cases and for other reasons in 73 (9.0%) cases. Completion rates are listed in Table 1 and adverse events are summarized in Table 2. Interim results of the OLE trial reported 86% of patients had an ADE with 18.7% (104 of the 556 initial patients) withdrawing from the study due to the event.[35] Overall discontinuance rate was 60%.

Central nervous system (CNS) disorders

As with most AEDs, central nervous system disorders are the most common ADEs with RTG.[8,9,34,35] Many had dose-response relationships and often occurred during the titration phase. These include dizziness, somnolence, headache, fatigue, confusional state, vertigo, disturbance in attention, memory impairment, diplopia and blurred vision. These were also the primary reasons for discontinuance: dizziness (5.7%), confusional state (3.9%), somnolence (3.4%) and fatigue (5.7%).[37] In the open-labeled extension trials of RESTORE 1 and 2, CNS-related ADEs were again the most commonly reported category occurring in 62% of patients.[35] These were primarily categorized as mild or moderate with the exception of 37 patients with serious CNS ADEs which included seizures, coma and status epilepticus.

Urinary/renal disorders

Because urinary bladder pathology was identified during toxicology studies in animals, ADEs pertaining to the urinary system were monitored during trials.[36] Subsequently, Rode and colleagues performed studies in rats that suggested KCNQ 4 and 5 are responsible for retigabine's bladder-relaxant effects.[38] In the placebo controlled trials (Phase IIb, RESTORE 1 and 2), the relative risk (RR) of experiencing a urinary/renal disorder was 1.32 (95% confidence interval [CI] 0.097–1.76) in the total RTG group and 1.05 (95% CI 0.714–1.543) in the 600 mg/day group, 0.995 (95% CI 0.67–1.478) in the 900 mg/day group, and 1.948 (95% CI 1.409–2.695) in the 1200 mg/day group.[36] In the pooled data from all phase II/III and OLE studies, 351 of the 1365 (25.7%) patients receiving RTG reported a urinary/renal ADE. The most common were urinary tract infection (UTI) (7.8%), urinary hesitation (3.1%), abnormal urinalysis (2.6%), dysuria (2.4%) and urinary retention (1.9%). The investigators determined that the majority of urinary/renal ADEs were mild and most patients continued treatment, but six patients (0.4%) withdrew for urinary retention and one patient for urinary retention and hesitation. In the placebo controlled trials, UTI-related ADEs were reported in 8.9% and 7.7% of RTG and placebo groups, respectively. A risk evaluation and mitigation strategy (REMS) regarding the risk of urinary retention and symptoms of acute urinary retention was instituted at the time of approval of RTG in the US.[39] In the OLE trials of RESTORE 1 and 2, 12% of the patients reported urinary and renal disorders: urinary retention (3%), urinary hesitation (3%),

urinary tract disorder (<1%), and decreased urine flow (<1%).[35] Close monitoring is recommended for high risk patients, including those taking concomitant medications that cause urinary retention and those unable to communicate clinical symptoms.[26]

Suicidal ideation

In December 2008, the FDA issued a public health advisory regarding suicidal behavior and ideation and AEDs following a retrospective analysis of 199 clinical trials of 11 antiepileptic drugs (carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproate and zonisamide) used in mono- and adjunctive therapies for epilepsy (25%), psychiatric indications (27%) and other conditions (48%).[40] The analysis indicated that those receiving AEDs had a risk of suicidal behavior or ideation of 0.43% compared to 0.24% for those receiving placebo. It required all manufacturers of AEDs to add a new section in the warnings section of their labeling and develop a medication guide for patients regarding risks of suicidal ideation and behavior. The ad hoc task force of the Commission on Neuropsychobiology of the International League Against Epilepsy reviewed the literature and documented concerns with the FDA meta-analysis and other subsequent related studies.[41] It concluded that suicidality in epilepsy is multifactorial, that certain AEDs may be associated with psychiatric problems leading to suicidal ideation and behavior, and new strategies should be implemented in controlled studies of new AEDs to better screen for suicide. No completed suicides, one suicidal ideation and one attempted suicide were reported in the RTG 1200 mg/day group and two cases of suicidal ideation were reported in the placebo group in the placebo controlled trials.[42] This translated to a rate of 2.5 patients with events per 1000 treated with RTG compared to 3.6 patients with events per 1000 patients with epilepsy in the FDA meta-analysis. Four additional cases were identified in the OLEs, one suicidal ideation, one injurious self-harm, and two attempted suicide by overdose.

QT interval/cardiac

Loss of function of the channel KCNQ1, which is expressed in the heart, results in long QT syndrome.[43,44] RTG is not active at this channel. In all published phase IIb, phase III and OLE trials to date, no abnormal trends were recorded on electrocardiogram.[8,9,34,35] A cardiac conduction study in healthy volunteers titrated to RTG 1200 mg/day and moxifloxacin produced a mean QT prolongation of 7.7-msec within 3 hours.[26] Therefore, it is recommended to monitor QT interval in patients with concomitant medications which prolong QT interval, congestive heart failure, ventricular hypertrophy, hypokalemia or hypomagnesemia.

Other

The FDA issued a warning in April 2013 that RTG can cause blue skin discoloration and pigment changes in the retina and it is unknown if these changes are reversible.[45] Skin discoloration has primarily been on or around the lips or nail beds of fingers or toes but there has been face and leg involvement as well. Skin discoloration usually occurred following four years of treatment, but may occur earlier. Retinal involvement may occur in the absence of skin abnormalities. The FDA recommended that baseline and periodic eye examinations include visual acuity testing and dilated fundus photography in patients taking RTG, and may include fluorescein angiograms, ocular coherence tomography, perimetry and electroretinograms. Puttnaik and Hughes recently found that the M-type current in monkey retinal pigment epithelium (RPE) was activated by 10 μM retigabine.[46] Their research also predicted that the M-type current in monkey RPE is most likely mediated by channels encoded by KCNQ4 and KCNQ5 subunits. Potassium channels effect retinal adhesion by providing the driving force for absorption of subretinal fluid and regulate RPE cell volume.

Interactions

With other anticonvulsants

In two open-label, single site, non-randomized, inpatient studies, RTG has been studied with concomitant AEDs in healthy men, one with lamotrigine and one with phenobarbital. Pharmacokinetic parameters of lamotrigine 200 mg single doses were compared before and after concomitant therapy with RTG titrated to a stable regimen of 600 mg/day (n = 15). RTG concomitant therapy decreased lamotrigine's $t_{1/2}$ and AUC by 15% and 18%, respectively, and increased Cl/F normalized by weight by 22% ($P = 0.001$ for all parameters).[47] Pharmacokinetic parameters of RTG 200 mg single doses were compared before and after

concomitant therapy with lamotrigine 25 mg/day (n = 14). Concomitant therapy resulted in an increase of RTG's $t_{1/2}$ and AUC of 7.5% (P = 0.045) and 15% (P = 0.006), respectively, and a decrease in Cl/F by 13% (P = 0.06). Both drugs are primarily metabolized by N-glucuronidation and both are substrates for UGT1A4. RTG is not known to induce enzymes, and metabolic competition is unlikely because of the high capacity of the UGT system. The authors speculated that the interaction may result from competition for renal elimination. With the exception of an increase in RTG's half-live of 23%, pharmacokinetic parameters were similar for RTG before and with concomitant therapy with phenobarbital 90 mg/day (n = 15).[48] No dosage adjustment is recommended for either medication.[26]

Sixty patients with epilepsy on stable monotherapy with valproic acid, topiramate, phenytoin or carbamazepine were given concomitant therapy with RTG and tapered off of their initial AED.[49] The pharmacokinetic profile of RTG was not altered by concomitant therapy with valproic acid or topiramate; but the clearance of RTG was increased by phenytoin and carbamazepine. RTG did not influence the pharmacokinetics of the other AEDs. It is recommended to increase the dose of RTG when carbamazepine or phenytoin is added to RTG therapy.[26]

Confidence intervals (CIs) were used to compare trough concentrations of concomitant AEDs (carbamazepine, clobazam, clonazepam, gabapentin, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, topiramate, valproic acid and zonisamide) prior to and during RTG treatment in RESTORE 1 and 2.[50] Clobazam, clonazepam, gabapentin and lamotrigine had 90% CIs that overlapped equivalence limits. RTG decreased lamotrigine's concentration by 20% which translated to a 90% CI excluding unity.

With other medications

The interaction of RTG and oral contraceptives has been investigated in two studies. RTG 450 mg per day did not alter the pharmacokinetic profile of a low dose oral contraceptive consisting of ethinyl estradiol and norgestrel (n = 18).[51] These results were confirmed in a second study of healthy women with an oral contraceptive containing 1 mg norethindrone and 0.035 mg ethinyl estradiol when RTG was titrated to 750 mg per day (n = 30).[52]

In-vitro data showed that digoxin's renal clearance was inhibited in a concentration-dependent manner by NAMR, an inhibitor of P-glycoprotein.[26] This impact has been investigated in an open label pharmacokinetic trial with 30 healthy volunteers and results have not been published.[53]

Ethanol

The effects of ethanol were examined in a randomized, 4-way crossover study in healthy volunteers aged 19–55 years (n = 17) who were moderate drinkers.[54] Moderate drinking was defined as consuming 7 to 28 drinks per week with ≥5 standard drinks (l.5 US fl oz of hard liquor, 5 fl oz of wine or 12 fl oz of beer) consumed in the past month on at least one occasion. Ethanol (1 gm/kg) or ethanol placebo (apple juice) were consumed within 20 minutes after a dose of RTG 200 mg or RTG placebo. Ethanol increased AUC and C_{max} of RTG by 36% and 23%, respectively, but RTG had no effect on ethanol's pharmacokinetic parameters. Most impairments were related to ethanol administration and were not increased by RTG with the exception of blurred vision. Patient's should be advised that RTG's adverse effects might be worsened with alcohol intake.[26]

Conclusions

RTG is a recently approved anticonvulsant with a unique site of action, low-threshold voltage-gated potassium channels. Randomized placebo-controlled trials reported median reduction in 28-day seizure frequency and responder rate for three doses, 600 mg, 900 mg, and 1200 mg/d in three divided doses in patients ≥ 16 years with refractory partial-onset seizures. It has limited drug interactions as it primarily undergoes glucuronidation and acetylation and is not metabolized through the cytochrome P450 system. It is not highly protein bound. Similar to other anticonvulsants, the majority of its ADEs are CNS related. RTG has several unique ADEs compared to other anticonvulsants: urinary retention, blue discoloration of the skin, and pigment changes in the retina. These effects are most likely due to RTG's effect on potassium channels. Retigabine's place in therapy is yet to be determined, especially with the recent revelations of effects on the retina with long-term use. Greater than 30% of patients with epilepsy have refractory seizures, reinforcing the need for new therapeutic options.

Author Contributions

Wrote the first draft of the manuscript: MYS. Wrote the manuscript: MYS. Developed the structure and arguments for the paper: MYS. Made critical revisions and approved final version: MYS. MYS reviewed and approved of the final manuscript.

Funding

Author discloses no funding sources.

Competing Interests

Dr. Splinter reports personal fees from Elsevier-Clinical Therapeutics, outside the submitted work.

Disclosures and Ethics

As a requirement of publication the author has provided signed confirmation of compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests. Provenance: the author was invited to submit this paper.

References

1. Food and Drug Administration. Potiga. 2013. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails. Accessed Jul 3, 2013.
2. European Medicines Agency. Trobalt. 2013. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001245/human_med_001431.jsp&mid=WC0b01ac058001d124. Accessed Jul 3, 2013.
3. Rundfeldt C, Netzer R. The novel anticonvulsant retigabine activates M-currents in Chinese hamster ovary-cells tranfected with human KCNQ2/3 subunits. *Neurosci Lett*. 2000;282:73–6.
4. Gunthorpe MJ, Large CH, Sankar R. The mechanism of action of retigabine (ezogabine), a first-in-class K + channel opener for the treatment of epilepsy. *Epilepsia*. 2012;53:412–24.
5. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med*. 2000;342:314–9.
6. Ngugi AK, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. Estimation of the burden of active and life-time epilepsy: A meta-analytic approach. *Epilepsia*. 2010;51:883–90.
7. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia*. 2010;51:1069–77.
8. Brodie MJ, Lerche H, Gil-Nagel A, et al. Efficacy and safety of adjunctive ezogabine (retigabine) in refractory partial epilepsy. *Neurology*. 2010; 75:1817–24.
9. French JA, Abou-Khalil BW, Leroy RF, et al. Randomized, double-blind, placebo-controlled trial of ezogabine (retigabine) in partial epilepsy. *Neurology*. 2011;76:1555–63.
10. Callaghan BC, Anand K, Hesdorffer D, Hauser WA, French JA. Likelihood of seizure remission in an adult population with refractory epilepsy. *Ann Neurol*. 2007;62:382–9.
11. Giussani G, Beghi E. Does mechanism of drug action matter to inform rational polytherapy in epilepsy? *CNS and Neurological Disorders—Drug Targets*. 2013;12:426–35.
12. Wang Q, Curran ME, Splawski I, et al. Positional cloning of a novel potassium channel gene: KVLQT1 mutations cause cardiac arrhythmias. *Nat Genet*. 1996;12:17–23.
13. Kubisch C, Schroeder BC, Friedrich T, et al. KCNQ4, a novel potassium channel expressed in sensory outer hair cells, is mutated in dominant deafness. *Cell*. 1999;96:437–46.
14. Singh NA, Charlier C, Stauffer D, et al. A novel potassium channel gene, KCNQ2, is mutated in an inherited epilepsy of newborns. *Nat Genet*. 1998;18:25–9.
15. Biervert C, Schroeder BC, Kubisch C, et al. A potassium channel mutation in neonatal human epilepsy. *Science*. 1998;279:403–6.
16. Charlier C, Singh NA, Ryan SG, et al. A pore mutation in a novel KQT-like potassium channel gene in an idiopathic epilepsy family. *Nat Genet*. 1998;18:53–5.
17. Tatulian L, Delmas P, Abogadie FC, Brown DA. Activation of expressed KCNQ potassium currents and native neuronal M-type potassium currents by the anti-convulsant drug retigabine. *J Neurosci*. 2001;21:5535–45.
18. Cooper EC, Jan LY. M-channels: Neurological diseases, neuromodulation, and drug development. *Arch Neurol*. 2003;60:496–500.
19. Wuttke TV, Seebohm G, Bail S, Maljevic S, Lerche H. The new anticonvulsant retigabine favors voltage-dependent opening of the Kv7.2 (KCNQ2) channel by binding to its activation gate. *Mol Pharmacol*. 2005;67:1009–17.
20. Large CH, Sokal DM, Nehlig A, et al. The spectrum of anticonvulsant efficacy of retigabine (ezogabine) in animal models: Implications for clinical use. *Epilepsia*. 2012;53:425–36.
21. Tober C, Rostock A, Rundfeldt C, Bartsch R. D-23129: A potent anticonvulsant in the amygdala kindling model of complex partial seizures. *Eur J Pharmacol*. 1996;303:163–9.
22. Mazarati A, Wu J, Shin D, Kwon YS, Sankar R. Antiepileptogenic and antiictogenic effects of retigabine under conditions of rapid kindling: An ontogenic study. *Epilepsia*. 2008;49:1777–86.
23. Bialer M, Johannessen SI, Levy RH, Perucca E, Tomson T, White HS. Progress report on new antiepileptic drugs: A summary of the Ninth Eilat Conference (EILAT IX). *Epilepsy Res*. 2009;83:1–43.
24. Rostock A, Tober C, Rundfeldt C, et al. D-23129: A new anticonvulsant with a broad spectrum activity in animal models of epileptic seizures. *Epilepsy Res*. 1996;23:211–23.
25. Ferron GM, Paul J, Fruncillo R, et al. Multiple-dose, linear, dose-proportional pharmacokinetics of retigabine in healthy volunteers. *J Clin Pharmacol*. 2002;42:175–82.
26. Potiga (ezogabine) tablets [product information]. 2013. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022345s007lbl.pdf. Accessed Jul 3, 2013.
27. Hempel R, Schupke H, McNeilly PJ, et al. Metabolism of retigabine (D-23129), a novel anticonvulsant. *Drug Metab Dispos*. 1999;27:613–22.
28. Hiller A, Nguyen N, Strassburg CP, et al. Retigabine N-glucuronidation and its potential role in enterohepatic circulation. *Drug Metab Dispos*. 1999;27:605–12.
29. Borlak J, Gasparic A, Locher M, Schupke H, Hermann R. N-Glucuronidation of the antiepileptic drug retigabine: results from studies with human volunteers, heterologously expressed human UGTs, human liver, kidney, and liver microsomal membranes of Crigler-Najjar type II. *Metabolism*. 2006;55:711–21.
30. Knebel NG, Grieb S, Leisenheimer S, Locher M. Determination of retigabine and its acetyl metabolite in biological matrices by on-line solid-phase extraction (column switching) liquid chromatography with tandem mass spectrometry. *J Chromatogr B Biomed Sci Appl*. 2000;748:97–111.
31. Hermann R, Ferron GM, Erb K, et al. Effects of age and sex on the disposition of retigabine. *Clin Pharmacol Ther*. 2003;73:61–70.

32. Shin P, Loewen G, Mansbach H, et al. Effect of renal impairment on retigabine pharmacokinetics [abstract no. 1.265]. *Epilepsia*. 2008;49(Suppl 7):116.
33. Mansbach H, Loewen G, Shin P, Marbury T, Kirby LC, Riff DS. Effect of hepatic impairment on retigabine pharmacokintics [abstract 1.260]. *Epilepsia*. 2008;49(Suppl 7):114.
34. Porter RJ, Partiot A, Sachdeo R, Nohria V, Alves WM. Randomized, multicenter, dose-ranging trial of retigabine for partial-onset seizures. *Neurology*. 2007;68:1197–204.
35. Gil-Nagel A, Brodie MJ, Leroy R, et al. Safety and efficacy of ezogabine (retigabine) in adults with refractory partial-onset seizures: Interim results from two ongoing open-label studies. *Epilepsy Res*. 2012;102:117–21.
36. Brickel N, Gandhi P, VanLandingham K, Hammond J, DeRossett S. The urinary safety profile and secondary renal effects of retigabine (ezogabine): A first-in-class antiepileptic drug that targets KCNQ (Kv7) potassium channels. *Epilepsia*. 2012;53:606–12.
37. Mula M. Recent and future antiepileptic drugs and their impact on cognition: What can we expect? *Expert Review of Neurotherapeutics*. 2012;12: 667–71.
38. Rode F, Svalo J, Sheykhzade M, Ronn LCB. Functional effects of the KCNQ modulators retigabine and XE991 in the rat urinary bladder. *Eur J Pharmacol*. 2010;638:121–7.
39. Potiga Risk Evaluation and Mitigation Strategy (REMS). 2011. http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM261933.pdf. Accessed Feb 8, 2012.
40. FDA Alert [1/31/2008;Updated:12/16/2008]. Information for Healthcare Professionals: Suicidal Behavior and Ideation and Antiepileptic Drugs. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm100192.htm. Accessed July 10, 2013.
41. Mula M, Kanner AM, Schmitz B, Schachter S. Antiepileptic drugs and suicidality: An expert consensus statement from the Task Force on Therapeutic Strategies of the ILAE Commission on Neuropsychobiology. *Epilepsia*. 2013;54:199–203.
42. Van Landingham K, Brickel N, De Rossett S. An analysis of the potential for suicidality with ezogabine (retigabine). *Neurology*. 2012;78(1) (Meeting Abstract).
43. Feldman AE, Gidal BE. QTc prolongation by antiepileptic drugs and the risk of torsade de pointes in patients with epilepsy. *Epilepsy Behav*. 2013;26:421–6.
44. Jentsch TJ. Neuronal KCNQ potassium channels: physiology and role in disease. *Nat Rev Neurosci*. 2000;1:21–30.
45. FDA [4/26/2013]. Potiga (Ezogabine): Drug Safety Communication—Linked To Retinal Abnormalities And Blue Skin Discoloration. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm349847.htm. Accessed Jul 10, 2013.
46. Pattnaik BR, Hughes BA. Effects of KCNQ channel modulators on the M-type potassium current in primate retinal pigment epithelium. *Am J Physiol Cell Physiol*. 2012;302:821–33.
47. Hermann R, Knebel NG, Niebch G, Richards L, Borlak J, Locher M. Pharmacokinetic interaction between retigabine and lamotrigine in healthy subjects. *Eur J Clin Pharmacol*. 2003;58:795–802.
48. Ferron GM, Patat A, Parks V, Rolan P, Troy SM. Lack of pharmacokinetic interaction between retigabine and phenobarbitone at steady-state in healthy subjects. *Br J Clin Pharmacol*. 2003;56:39–45.
49. Ferron GM, Sachdeo R, Partiot A, Fritz T, Althouse S, Troy S. Pharmacokinetic interaction between valproic acid, topiramate, phenytoin or carbamazepine and retigabine in epileptic patients. *Clin Pharmacol Ther*. 2001;69(2):P18.
50. Tompson DJ, Vanlandingham KE. The effects of retigabine on the pharmacokinetics of concomitantly administered antiepileptic drugs. *Epilepsia*. 2010;51(Suppl 4):123–4.
51. Paul J, Ferron GM, Richards L, Getsy J, Troy SM. Retigabine does not alter the pharmacokinetics of a low-dose oral contraceptive in women. *Neurology*. 2001;56(Suppl 3):A335–6.
52. Hansen H, Loewen G, Shin P, Mansbach H. Lack of significant pharmacokinetic interaction between retigabine and oral contraceptive hormones. *Epilepsia*. 2008;49(Suppl 7):113.
53. An Open-label, Single-centre Study Evaluating the Pharmacokinetics of Digoxin Alone and When Administered at Various Doses of Ezogabine/Retigabine in Healthy Adults. The Pharmacokinetics of Ezogabine/Retigabine and the N-acetyl Metabolite of Ezogabine/Retigabine (NAMR) Will Also be Assessed. http://clinicaltrials.gov/ct2/show/study/NCT01583036?term=retigabine&rank=3. Accessed Jul 15, 2013.
54. Crean CS, Tompson DJ. The effects of ethanol on the pharmacokinetics, pharmacodynamics, safety, and tolerability of ezogabine (retigabine). *Clin Ther*. 2013;35:87–93.