Randomized, Double-Blind, Placebo-Controlled Trial of Ezogabine (Retigabine) in Partial Epilepsy.


OBJECTIVE: To evaluate the efficacy and safety of ezogabine (United States adopted name)/retigabine (international nonproprietary name) (EZG[RTG]) 1,200 mg/day as adjunctive treatment in adults with drug-resistant epilepsy with partial-onset seizures with or without secondary generalization. METHODS: RESTORE 1 was a multicenter, randomized, double-blind, parallel-group trial. Following a prospective 8-week baseline phase, patients entered an 18-week double-blind treatment period (6-week forced dose titration to EZG[RTG] 1,200 mg/day in 3 equally divided doses or placebo, followed by a 12-week maintenance phase). Results were analyzed on an intent-to-treat basis for the entire 18-week period and for patients reaching the maintenance phase. RESULTS: In 306 patients randomized, 305 received EZG(RTG) 1,200 mg/day (n = 153) or placebo (n = 152). Median percent reduction in total partial-seizure frequency was 44.3% vs 17.5% (p < 0.001) for EZG(RTG) and placebo, respectively, during the 18-week double-blind period; responder rates (≥50% reduction in total partial-seizure frequency from baseline) were 44.4% vs 17.8% (p < 0.001). In 256 patients (EZG[RTG], 119; placebo, 137) entering the 12-week maintenance phase, median percent reduction in seizure frequency for EZG(RTG) vs placebo was 54.5% and 18.9% (p < 0.001), respectively; responder rates were 55.5% vs 22.6% (p < 0.001). The proportion of patients discontinuing due to treatment-emergent adverse events (TEAEs) was 26.8% (EZG[RTG]) vs 8.6% (placebo). Dizziness, somnolence, fatigue, confusion, dysarthria, urinary tract infection, ataxia, and blurred vision were the most common TEAEs reported by more patients treated with EZG(RTG) than placebo. CONCLUSIONS: This study demonstrates that EZG(RTG) is effective as add-on therapy for reducing seizure frequency in patients with drug-resistant partial-onset seizures. CLASSIFICATION OF EVIDENCE: This study provides Class II evidence that EZG(RTG) 1,200 mg/day is effective as adjunctive therapy in adults with partial-onset seizures with or without secondary generalization.

Commentary

Ezogabine, the U.S.-adopted name of the compound formerly known as retigabine, is a first-in-class neuronal potassium channel opener for which two phase 3 pivotal trials have been completed, both of which show significant results in reducing seizure frequency compared with placebo in adults with refractory partial onset epilepsy.

The study discussed herein, the RESTORE 1 trial (1), consists of a forced-titration of ezogabine over 6 weeks to a dose of 1,200 mg per day, after a prospective 8-week baseline, and followed by a 12-week maintenance phase. Twenty-two percent of ezogabine-treated subjects (34/153) did not enter the maintenance phase compared with 10% (15/152) of the placebo-treated subjects, discontinuing during the titration phase mostly as a result of adverse effects, the most common of which were dizziness, somnolence, fatigue, confusion, and urinary tract infection. Another 22 ezogabine-treated subjects discontinued during the maintenance phase (vs 10 in the placebo-treated arm), for a total completion rate of 63 percent in the active arm. Twenty-seven percent of ezogabine subjects discontinued because of adverse effects compared with 9 percent in the placebo arm. One dose reduction to 1,050 mg per day was allowed to manage adverse effects. Because of the low completer rate, the potential for bias is great enough to downgrade this well-designed, adequately masked and blinded study to class 2. The drug also loses points on the ‘ease of use’ factor: ezogabine is administered three times per day.

Now let’s compare this to the results for ezogabine at lower doses. A clinical trial published in 2010, the RESTORE 2 study (2), evaluated ezogabine doses of 600 and 900 mg per day compared with placebo. The study had a similar design but had a forced titration over 4 weeks. Twenty-six percent of 179 subjects in the 900 mg treatment arm, 14 percent of 181 subjects in the 600 mg treatment arm, and 8 percent of placebo subjects discontinued because of adverse effects. Therefore, between 900 mg and 1,200 mg per day, there was no difference in discontinuing because of adverse effects. It should
Ezogabine AKA Retigabine: Is More Better? Trying to Find the Right Dose From Clinical Trials

be stated that discontinuation as a result of adverse effects is probably a reasonable surrogate measure for tolerability outside of the clinical trial setting.

What about efficacy? The efficacy within the narrow characteristics of the clinical trial population was clear and dose-related. For those who were in the maintenance phase (not including the titration phase) of ezogabine at 1,200 mg per day—which numbered 119 and only 97 of them completed—the mean percent seizure frequency reduction was 55 percent, and the responder rate was 56 percent. In the 600-mg-per-day arm during the 12-week maintenance phase, the mean seizure frequency reduction was 35 percent, with a responder rate of 37 percent; for the 900-mg-per-day arm, the findings were 44 percent and 47 percent. Therefore, for every 300 mg increase in total daily dose, another 10 percent in seizure reduction is gained. This is an amazing dose response. The results were a bit less robust but still proportional when the entire treatment period is analyzed, including both titration and maintenance phases. The seizure-free rates were not more impressive than the usual antiepileptic drug (AED) add-on trials, however.

Still, there is the other side of the coin; it is taken three times per day, has a high discontinuation rate because of side effects, and causes increased bladder postvoid residual and urinary tract infections. This adverse effect, which is the result of inhibition of bladder contractility from the effects of ezogabine on KCNQ2–5 channels in bladder muscle (3), will add a new consideration when we receive calls from confused hospital paging operators who are not sure if they are calling “neurology” or “urology.”

The translation of clinical trial data in epilepsy to clinical practice is subject to interpretation from all angles. Sometimes it appears that doses in clinical trials are lower than those that are effective in clinical practice. For example, gabapentin seemed not to be explored adequately at higher doses in clinical trials and was used at much higher doses by neurologists when it was first marketed. Topiramate was systematically evaluated in clinical trials up to 1,600 mg per day, a dose now thought to be outdated. Many AED trials are analyzed to show at which dose the study drug significantly separates from placebo, and it is declared that at this point in titration, evidence of efficacy is present. For example, for levetiracetam this could be at 1,000 mg per day after 2 weeks of titration and for topiramate at 100 to 150 mg per day after 1 to 2 weeks into titration. Whether this is a clinically meaningful finding or not is debatable, but the analysis provides a bit of insight into AED dosing.

Lamotrigine is approved for epilepsy at a dose of 500 mg per day. It is now well-appreciated that much lower doses can be effective, and many neurologist use lamotrigine levels and clinical response rather than dose to guide therapy in any case because of the individualized metabolism of lamotrigine. Levels of ezogabine may also prove to be useful.

Most AEDs considered efficacious are associated with a dose response, a reliable sign strongly suggesting that a drug has some action to stop seizures. Ezogabine certainly has this property. The 50 percent responder rates associated with the doses used in RESTORE 1 and 2 are among the highest we have seen in AED trials. But, where will the effective dose be for a partial epilepsy patient who has failed two AEDs? It will likely not be at 900 or 1,200 mg per day but perhaps much lower; the lower dose range certainly has a good chance of meaningfully reducing seizures and will be associated with less risk of side effects. For stalwarts who can tolerate the higher doses of ezogabine, the maximal efficacy was not revealed in these studies. Perhaps more is even better! Adverse effects are not dose-associated above 900 mg per day, according to these data sets. Inexplicably, there is a ceiling dose for adverse effect rates but not for efficacy.

Ezogabine is exciting—it has amazing efficacy and the potential for a completely new set of adverse effects, but perhaps lower doses will be effective in the general epilepsy population, and the adverse effect rate will certainly be less at lower doses. It scores poorly on the ease-of-use scale, though, because of the multiple daily dosing; refractory epilepsy patients are often key in to taking medications frequently, so perhaps this will be less of an issue than what it seems at face value. Patients with epilepsy certainly need new treatments that can reduce seizure frequency, and hopefully ezogabine will readily find a niche in the practice of epilepsy.

by Cynthia L. Harden, MD

References
Disclosure of Potential Conflicts of Interest

Instructions
The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.
   Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

2. The work under consideration for publication.
   This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. Relevant financial activities outside the submitted work.
   This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

   Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work’s sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

   For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Other relationships
   Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.
American Epilepsy Society

Epilepsy Currents Journal
Disclosure of Potential Conflicts of Interest

Section #1 Identifying Information

1. Today's Date: 2/10/2012

2. First Name Cynthia Last Name Harden Degree MD

3. Are you the Main Assigned Author? ☒ Yes ☐ No
   
   If no, enter your name as co-author:

4. Manuscript/Article Title: Ezogabine AKA Retigabine: Is More Better? Trying to Find the Right Dose From Clinical Trials

5. Journal Issue you are submitting for: 12.1

Section #2 The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

<table>
<thead>
<tr>
<th>Type</th>
<th>No</th>
<th>Money Paid to You</th>
<th>Money to Your Institution*</th>
<th>Name of Entity</th>
<th>Comments**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Grant</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Consulting fee or honorarium</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Support for travel to meetings for the study or other purposes</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Fees for participating in review activities such as data monitoring boards, statistical analysis, end point committees, and the like</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Payment for writing or reviewing the manuscript</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Provision of writing assistance, medicines, equipment, or administrative support.</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Other</td>
<td>☐</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* This means money that your institution received for your efforts on this study.

** Use this section to provide any needed explanation.
**Section #3 Relevant financial activities outside the submitted work.**

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the “Add” box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

<table>
<thead>
<tr>
<th>Type of relationship (in alphabetical order)</th>
<th>No</th>
<th>Money Paid to You</th>
<th>Money to Your Institution*</th>
<th>Name of Entity</th>
<th>Comments**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Board membership</td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Consultancy</td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Employment</td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Expert testimony</td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Grants/grants pending</td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Payment for lectures including service on speakers bureaus</td>
<td>☑</td>
<td>yes</td>
<td>UCB, Glaxo, Lundbeck</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Payment for manuscript preparation.</td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Patents (planned, pending or issued)</td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Royalties</td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Payment for development of educational presentations</td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Stock/stock options</td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Travel/accommodations/meeting expenses unrelated to activities listed.**</td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. Other (err on the side of full disclosure)</td>
<td>☑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

**Section #4 Other relationships**

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☐ No other relationships/conditions/circumstances that present a potential conflict of interest.
☑ Yes, the following relationships/conditions/circumstances are present:

Speaker's Bureau for Glaxo

Thank you for your assistance.

_Epilepsy Currents_ Editorial Board