

## RETIGABINE: HAS THE ORPHAN FOUND A HOME?

**Randomized, Multicenter, Dose-Ranging Trial of Retigabine for Partial-Onset Seizures.** Porter RJ, Partiot A, Sachdeo R, Nohria V, Alves WM; 205 Study Group. *Neurology* 2007;68(15):1197–1204. **OBJECTIVE:** To evaluate the efficacy and safety of retigabine 600, 900, and 1,200 mg/day administered three times daily as adjunctive therapy in patients with partial-onset seizures. **METHODS:** A multicenter, randomized, double-blind, placebo-controlled trial was performed. After an 8-week baseline phase, patients were randomized to a 16-week double-blind treatment period (8-week forced titration and 8-week maintenance) followed by either tapering or entry into an open-label extension study. Primary efficacy was the percentage change from baseline in monthly seizure frequency and compared across treatment arms. Secondary efficacy comparisons included the proportion of patients experiencing 50% reduction in seizure frequency (responder rate), emergence of new seizure types, and physician assessment of global clinical improvement. Safety/tolerability assessments included adverse events (AEs), physical and neurologic examinations, and clinical laboratory evaluations. Efficacy analyses were performed on the intent-to-treat population. **RESULTS:** Of the 399 randomized patients, 279 (69.9%) completed the double-blind treatment period. The median percent change in monthly total partial seizure frequency from baseline was –23% for 600 mg/day, –29% for 900 mg/day, and –35% for 1,200 mg/day vs –13% for placebo ( $p < 0.001$  for overall difference across all treatment arms). Responder rates for retigabine were 23% for 600 mg/day, 32% for 900 mg/day ( $p = 0.021$ ), and 33% for 1,200 mg/day ( $p = 0.016$ ), vs 16% for placebo. The most common treatment-emergent AEs were somnolence, dizziness, confusion, speech disorder, vertigo, tremor, amnesia, abnormal thinking, abnormal gait, paresthesia, and diplopia. **CONCLUSION:** Adjunctive therapy with retigabine is well tolerated and reduces the frequency of partial-onset seizures in a dose-dependent manner.

### COMMENTARY

Retigabine is an older agent among the new group of antiepileptic drugs (AEDs)—now involved in its second wave of development. It is the first drug of its class to be studied in clinical trials for any indication (1). Retigabine was initially created and developed by a Former East Germany company and then licensed to a U.S. company for development as an antiepileptic drug in the late 1990s (and finally, to yet another one 3 years ago). During the period of the late 1990s, there was much excitement because retigabine was found to be effective in almost all animal models tested, such as maximal electroshock, pentylenetetrazol, NMDA, picrotoxin-induced seizures, amygdala kindling, and sound-induced seizures in epilepsy-prone rats (1–7). Expectations were high, in light of the animal studies, that it must be a broad spectrum AED.

The phase I trials in normal healthy volunteers were successful, allowing the development of retigabine to proceed and clinical trials for epilepsy were begun. The Porter et al. article reports the first double-blind, randomized clinical trial of retigabine in patients with refractory partial epilepsy. The U.S. drug company that is now working on retigabine as a new AED, initially for partial-onset seizures, appears to be committed to its development as an antiepileptic agent.

What is so interesting about this compound? First of all, it has an unusual mechanism of action, which was well known before clinical trials began, with over 100 preclinical publications providing information on the drug. Retigabine's main

mechanism of action is M current modulation—a potassium conductance regulating excitability in neuronal cells (8,9). Its effect occurs by acting on the KCNQ2 and KCNQ3 channels. To date, 5 KCNQ channels have been cloned (2–5,10). Retigabine activates KCNQ2 and KCNQ3. Mutations of these channels have been implicated in human hereditary diseases: benign familial neonatal convulsions (KCNQ2 and KCNQ3) (10), deafness (KCNQ4), and possibly, retinal degeneration (KCNQ5) (7). In addition, retigabine potentiates GABA-evoked channels in high concentrations, causes blockade of 4-aminopyridine-induced stimulation of glutamine release, and stimulates GABA synthesis in rat hippocampus (11).

The drug, as currently formulated, has a short half-life, requiring three times a day dosing in the trials. In the present trial, doses of 600, 900, and 1200 mg were explored for efficacy and tolerability in patients > 18 years. Although the drug might be effective in other seizure types, the study only evaluated its effects on partial-onset seizures. The investigators found that retigabine reduced seizures in this refractory group at a rate similar to other new antiepileptic drugs (12). The data indicate that 900 mg probably will be the median dose for this drug, as it produced fewer adverse effects than the 1200-mg dose (17% for the 600 mg arm, 20.2% for the 900 mg arm, and 29.2% for the 1200 mg arm). The adverse effects seem to be dose related and were mainly CNS generated. No hypersensitivity reaction was observed, which is a positive sign.

Currently, there are two ongoing phase III trials, which were designed to try to elucidate issues raised in the Phase II trial concerning efficacy and tolerability, quality of life, and seizure severity. Hopefully, these trials will be available for scrutiny in 1 to 2 years (<http://clinicaltrials.gov/>).

Although there are 10 new AEDs available (in addition to one or two more soon to be approved, and others, like retigabine, in clinical trials) as well as treatment options, such as vagus nerve stimulation and epilepsy surgery, an unacceptable number of patients continue to live with refractory seizures. It is interesting to contemplate why this is so. Why is it that drugs with widely different mechanisms of action produce similar results in clinical trials (10); and why are some drugs so effective in animal models of epilepsy and then only moderately effective in humans, such as evidenced in the Phase II trial by Porter and colleagues?

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