Perampanel: Getting AMPed for AMPA Targets

Randomized Phase III Study 306: Adjunctive Perampanel for Refractory Partial-Onset Seizures.

Krauss GL, Serratosa JM, Villanueva V, Endziniene M, Hong Z, French J, Yang H, Squillacote D, Edwards HB, Zhu J, Laurenza A. *Neurology* 2012;78:1408–1415.

OBJECTIVE: To evaluate the efficacy and safety of perampanel 2, 4, and 8 mg/day added to 1–3 concomitant antiepileptic drugs (AEDs) in patients with uncontrolled partial-onset seizures. METHODS: During this double-blind, placebo-controlled trial, patients with persisting seizures on 1–3 AEDs were randomized to perampanel 2, 4, and 8 mg/day or placebo following a 6-week baseline phase. Perampanel was titrated weekly by 2 mg/day and maintained at the dose achieved for 13 weeks. Primary endpoints were median percent change in seizure frequency and 50% responder rate. Analysis of covariance was performed on all treated patients with any seizure data (recorded in daily diaries) in the double-blind phase. RESULTS: A total of 706 patients were randomized and received trial medication; 623 completed the trial. Median percent change in seizure frequency—the primary efficacy endpoint—was -10.7%, -13.6%, -23.3%, and -30.8% for placebo, perampanel 2, 4, and 8 mg/day, respectively. The difference from placebo was statistically significant for perampanel 4 mg/day ($p = 0.0026$) and 8 mg/day ($p < 0.0001$). The corresponding 50% responder rates were 17.9%, 20.6%, 28.5%, and 34.9%. The difference from placebo was statistically significant for perampanel 4 mg/day ($p = 0.0132$) and 8 mg/day ($p = 0.0003$). An apparent dose response was suggested for dizziness, which was the most frequent treatment-emergent adverse event. CONCLUSIONS: This trial demonstrated that adjunctive perampanel effectively reduced seizure frequency and possessed a favorable tolerability profile in patients ≥ 12 years with partial-onset seizures (with or without secondary generalization), with a minimum effective dose of 4 mg/day. CLASSIFICATION OF EVIDENCE: This study provides Class I evidence that 4 and 8 mg/day doses of adjunctive perampanel are effective and tolerated in reducing partial-onset seizures.

Commentary

In the April 18 issue of the journal *Neurology*, Dr. Krauss and an international group of investigators presented the results of a multicenter, double-blind, placebo-controlled, randomized dose response trial of perampanel used as adjunct to other antiepileptic drugs (AEDs) in patients with refractory partial-onset seizures (1). Perampanel, a new AED currently undergoing investigation, showed a unique mechanism of action: postsynaptic AMPA receptor antagonism (1, 2–5). Because this is the first agent to function in this manner—as well as the multinational aspect of the investigation—this particular study is distinctive. Thus, it is important to examine the study in detail and these characteristics specifically to fully grasp the impactful nature of the manuscript.

The goal of this particular trial was to evaluate the efficacy, dose response, and safety of a single daily dose of 2, 4, and 8 mg of add-on perampanel when added to up to one to three antiepileptic drugs in patients 12 years and older with drug resistant partial-onset seizures. This global trial encompassed 116 centers across 24 countries over Europe, Asia, and Australia. Patients from Germany, Bulgaria, Portugal, Lithuania, India, and China were enrolled in this particular study (1).

The methodology for this study is familiar for epilepsy trials: There was a six-week baseline requiring a minimum of five partial seizures for each patient for inclusion and up to three concurrent antiepileptic drugs; Vagus nerve stimulation could also be included. Patients were then randomized in a 1:1 ratio to four different groups: placebo; 2 mg; 4 mg; and 8 mg. The drug was initiated if they were in one of the medication groups on an escalating dose of 2 mg per day/per week of perampanel up to the randomized dose to which they were allocated. After six weeks of baseline, there were six weeks of titration, and then 13 weeks of maintenance and follow-up (1). The primary outcome was the percent of change in seizure frequency per 28-day period compared to baseline and in comparison to the placebo group. Responder rate, which is the percent of patients with 50% reduction in seizures, was also assessed.

Of 818 patients screened, 712 individuals were ultimately randomized, 706 were included in the safety analysis, and 705 in the intention to treat analysis (1). Investigators found a significant reduction in partial-onset seizures as compared to placebo in the 4 and 8 mg groups, with 4 mg reducing seizures by 23.3% and 8 mg by 30.8% versus 10.7% for placebo and 13.6% for 2 mg (1). The responder rate was 17.9% for placebo,

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20.6% for 2 mg, 4 mg at 28.5%, and 8 mg at 34.9%. Concurrent seizure-free rates were 1.2% for placebo, 1.9% for 2 mg, 4.4% for 4 mg, and 4.8% for 8 mg with no significance between these groups (1).

Primary adverse effects included dizziness, somnolence, fatigue, and gait disturbance. Dizziness was the most common effect and appeared to be dose related. No deaths were reported. Adverse effects that led to early discontinuation included dizziness, convulsions or increased seizures, fatigue, and vertigo (1). The percentage of patients with a seizure increase were 15% for placebo, 11% for 2 mg, 8% for 4 mg, and 8% for 8 mg with no significant difference (1). There was one report of suicidality but no completed suicides were noted. There were no clinically meaningful changes in lab results or vital signs. There was a slightly higher increase in weight compared to placebo, but there were no changes in EKG, and there was a low incidence of rash.

The researchers concluded that the minimal effective dose of perampanel was 4 mg with benefit up to 8 mg. The drug has simple pharmacology with steady state concentration reached in 14 days and a half-life of 70 to 120 hours per day allowing for single daily dosing. As for drug interactions, carbamazepine, oxcarbazepine, and phenytoin are inducers of perampanel metabolism and, therefore, perampanel may decrease serum concentrations of these agents.

Perampanel exerts its effects on glutamate receptors (1–5). Glutamate, an excitatory neurotransmitter, binds a series of ionotropic postsynaptic receptors that mediate its impact on neuronal excitability (2). These receptors are known as AMPA, kainate, and NMDA (2). Perampanel is the first agent of its kind to target the AMPA receptor (1–5). Thus, the positive study results from this trial affirm this molecular approach to tackling seizures with expectations for other drugs similarly designed. In sum, this AED opens up a new doorway to a class of medications.

This trial also represents a transnational randomized study. Theoretically, this universal approach provides a more representative evaluation of a novel drug across a multitude of ethnic and diverse populations of individuals. However, this has not been without problems: In other perampanel analyses also evaluating add-on treatment—at higher doses of 8 mg and 12 mg—the placebo rate for those trials showed a high responder rate for the placebo group, making it more difficult to discern the true benefit of the agent (5). Upon further evaluation, it was found that the elevated responder rate for the placebo group could be pinpointed to certain countries and regions (5). This illuminates a fundamental but vexing problem: Relying on seizure self-reporting as a primary outcome measure of efficacy is not sufficient. Without a more standardized biomarker—and given considerable heterogeneity in epilepsy diagnosis and management across numerous cultures and health systems—this global clinical trial method creates concern that detecting a beneficial signal will not be readily apparent as was ultimately demonstrated with 8 mg and 12 mg doses of perampanel. Nevertheless, this current study highlights that worldwide trials are feasible and can meet their primary outcome. Until the agent is approved and available, questions will remain regarding whether global trials better approximate clinical effectiveness.

The most obvious and important question to arise from this paper is whether this drug represents a game changer in the management of seizures. Perhaps the answer to that question can be gleaned by considering previous experience of bringing new AEDs to market. Twenty years ago, in 1992, antiepileptic drugs consisted primarily of a handful of compounds such as phenobarbital, phenytoin, valproic acid, and carbamazepine. During that time, AED discussions were dominated by talk of two new agents soon to come onto the U.S. market and transform the field: felbamate and gabapentin. In particular, gabapentin was designed in the lab to specifically increase GABA and was thought to have a clear mechanism of action, as evidenced by the GABA mention in its name. From this, the concept of compounds with different mechanisms of actions being paired—otherwise known as rational polytherapy—flourished. The idea was to choose medications based on their mechanism of action so that we could see additive or synergistic effects. Theoretically, pharmacological management of epilepsy would change.

All epilepsy specialists know what happened next: Felbamate was relegated to a second-line agent, and gabapentin became a blockbuster drug for everything *but* seizures. Adding insult to injury, its mechanism of action was found to be something other than designed. Several questions beg to be asked: Is our past prologue? Does perampanel, with its new mechanism of action and first-in-class agent status, represent an improvement in effectiveness—or will it suffer the fate of other promising AEDs that were once amped yet fell into disuse? Once again, we hear discussions about rational polytherapy, especially in light of recently approved agents—such as ezogabine and lacosamide—with novel mechanisms of action. Is 2012–2013 an inflection point in terms of changing the practice of epilepsy therapeutics? The answer is not known. We can only hope, on behalf of our patients, that this AED lives up to the promise and excitement it has engendered in the epilepsy community at large.

by Joseph I. Sirven, MD

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