Journal Club:

Randomized phase III study 306

Adjunctive perampanel for refractory partial-onset seizures

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BACKGROUND AND SIGNIFICANCE A working understanding of antiepileptic drug development, critical appraisal of drug trial design, and interpretation of study results are fundamental for the neurologist and epileptologist, to incorporate newer anticonvulsant medications into clinical practice. In this Journal Club, we evaluate a phase III study by Krauss et al.¹ that demonstrates efficacy and safety of adjunctive perampanel for refractory partial-onset seizures.

Perampanel is a highly selective, noncompetitive α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)-type glutamate receptor antagonist. AMPA receptors mediate the excitatory actions of glutamate and are essential in the generation and spread of epileptic activity.² Development of other related glutamate receptor antagonists as potential anticonvulsants, including *N*-methyl-D-aspartic acid receptor antagonists and other AMPA receptor antagonists, has been disappointing.² However, interest in perampanel has escalated, because it has been shown to reduce seizure activity in several animal models of epilepsy,³ and preliminary safety and tolerability of oral perampanel (2–12 mg/d) have been demonstrated in 2 phase II dose-escalation, placebo-controlled studies.⁴ This study adds Class I evidence of the efficacy and safety of adjunctive perampanel at 4 and 8 mg/d doses in reducing partial onset seizures. Such controlled phase III trials are required, in part, by regulatory agencies before consideration for approved clinical use.

HYPOTHESIS AND DESIGN The essential question being investigated is whether perampanel, a drug with a unique mechanism of action, is a potentially valuable medication for the treatment of epilepsy. This is a relevant question, because despite the near yearly introduction of new antiepileptic drugs, more than a third of patients with epilepsy continue to be medication-refractory.⁵

Specifically, the investigators focused on obtaining data on the efficacy and safety of adjunctive perampanel within their study population. Efficacy refers to measured improvement within the narrow predefined

boundaries of the clinical trial. In this case, the boundaries defined a specific patient population being treated with a preset dosing of perampanel as those 12 years of age and older with medication-refractory partial onset seizures, and excluding patients according to predetermined listed criteria. Patients were followed for 19 weeks in the double-blind treatment phase. Doses and titration were defined to evaluate the dose response.

The design set forth by the investigators optimized its feasibility for completion of the study. The study recruited adults and children 12 years and older with medication-refractory partial seizures. End points for defining efficacy were specified to be seizure count reduction and responder rate (percentage of patients who experienced a 50% or greater reduction in seizure frequency) in order to reduce the sample size needed to demonstrate significant treatment differences. If an end point of seizure freedom was chosen, this would have required a larger study population, because seizure freedom would be expected to occur in only a small subset of patients already proven to be medication-refractory.

METHODS Patients aged 12 years and older from 116 centers in 24 countries with refractory simple partial or complex partial seizures, with or without secondary generalization, were enrolled. Subjects were taking 1 to 3 antiepileptic drugs and were randomized if they had at least 5 partial seizures in the 6-week baseline period. This was followed by a 19-week treatment phase (6-week titration and 13-week maintenance period) with either adjunctive placebo or perampanel in doses of 2, 4, or 8 mg/d. Higher dose treatment groups (4 and 8 mg/d) were titrated at 2 mg/d each week to the respective goal doses.

The primary end points were the percentage change in seizure frequency per 28 days based on seizure counts from patient diaries and responder rate, defined as the fraction of patients with a 50% or more reduction in seizure frequency. Percentage change in frequency of seizures and dose-response analysis of percentage change in seizures were used as secondary end points.

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Safety was assessed using proactive reporting of adverse effects using questionnaires, laboratory results, and physical examination.

RESULTS Of the 706 patients appropriately randomized, 623 patients completed the study, and 83 did not, including 32 because of adverse events. The median seizure frequency during the 6-week baseline period was 9.3 to 10.9 seizures per 28 days.

The median percentage change in seizure frequency was -10.7% for placebo, -13.6% for 2 mg/d, -23.3% for 4 mg/d, and -30.8% for 8 mg/d, with statistically significant p values for 4 mg/d ($p = 0.003$) and 8 mg/d ($p < 0.001$) groups compared with placebo by rank-transformed analysis of covariance. Because of the skewed distribution of seizure frequency, data at baseline and seizure per 28 days during treatment were rank transformed before regression analysis. The 50% responder rate was 17.9% for placebo group and 20.6%, 28.5%, and 34.9% for the 2, 4, and 8 mg/d perampanel groups, respectively. The 4 mg/d ($p = 0.013$) and 8 mg/d ($p < 0.001$) groups were statistically different from the placebo group. Seizure freedom rates were 1.2% for placebo, and 1.9%, 4.4%, and 4.8% for the 2-, 4-, and 8-mg perampanel groups.

Dizziness, fatigue, gait disturbance, and somnolence were the most frequently reported side effects, which were mostly mild or moderate, with some rates twice as high in perampanel groups compared with placebo. A dose-related increase in side effects was seen in the treatment groups. The rates reported for dizziness were 9.7% in placebo and 10.0%, 16.3%, and 26.6% in 2-, 4-, and 8-mg perampanel groups, respectively. Worsening seizures ($>50\%$ increase from baseline) were reported in 15%, 11%, 8%, and 8% of patients treated with placebo, 2, 4, and 8 mg of perampanel, respectively. Side effects leading to discontinuation from the study (dizziness, convolution, fatigue, and vertigo) occurred in 3.8%, 6.7%, 2.9%, and 7.1% with placebo, 2, 4, and 8 mg of perampanel, respectively. No deaths were reported and seizures were the only serious side effect reported in more than 1 group (5 cases in placebo and 2 cases in the 2 mg/d group). No significant changes in laboratory values between groups, vital signs, or EKG parameters were reported.

INTERPRETATION The strength of this study is that it is a randomized, placebo-controlled, double-blinded study. This is the most rigorous way to obtain reproducible data that are both valid and precise. The study was able to generate statistically significant results. There was a linear dose-response relationship with superiority of the test agent compared with placebo. The efficacy and tolerability profile were similar to trial results of newer antiepileptic drugs already in use.

The demonstration of efficacy within a clinical trial does not always translate into clinical effectiveness. Patient populations selected for clinical trials differ from the general patient population, thus results may not always be generalized into clinical practice. In addition, if enhanced clinical efficacy incurs intolerable side effects, this will also diminish the clinical effectiveness. Finally, the 19-week length of the clinical trial demonstrated early efficacy, but it does not offer evidence regarding the long-term durability of the drug's benefit.

The weaknesses of this study are inherent to clinical trials studying the treatment of epilepsy. This includes restrictions to a specific population, dosing regimen, and follow-up duration. In particular, for practical and logistical reasons, children were excluded, leaving clinicians again in the position of extrapolating information from a study to a unique and understudied population.⁶ In addition, the results are dependent on patient self-reporting using seizure diaries, which are subject to individual variability in complete and accurate reporting.

The study was not powered to detect rare or serious side effects such as Stevens-Johnson syndrome, aplastic anemia, or liver failure, that occur with other anticonvulsant medications. Because adverse events occurred in a dose-dependent manner, it is possible that blinding was compromised. In fact, this is a recurrent issue in anti-convulsant drug trials that has been under-recognized. Finally, it should be noted that the lead author is a consultant for Eisai Inc. However, knowledgeable investigators are often recruited to participate in study design and conduct, and therefore develop consulting relationships with sponsors of clinical trials.

The authors conclude that the utility of perampanel, at a minimal effective dose of 4 mg, as an adjunctive treatment of uncontrolled partial-onset seizures, is promising, and this is supported by the results of the study. Translation of its use into clinical practice will depend partly on logistical issues—whether further studies can validate these published results. Assessment of clinical effectiveness will also be a key factor. Further research, including prospective, open-label studies and retrospective studies, with additional experience in clinical practice, will reveal the usefulness of perampanel over time. The long-term efficacy and the possible emergence of adverse events not seen during the study period are also important data that will contribute to its use in clinical practice.

In conclusion, the results of this study demonstrating efficacy and safety are a first step to determining whether perampanel will be a valuable adjunctive medication in the clinical care of patients with epilepsy. Perampanel seems to possess properties that are desired in the ideal anticonvulsant medication, including efficacy, modest side effects, and long half-life allowing once a day dosing. The continued

critical appraisal of this study and those studies to follow will allow clinicians to continue to make scientific and practical decisions in clinical practice.

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DISCLOSURE

M. Pulicken, D. Hsieh, and D. Hoch report no disclosures. A. Cole serves as a consultant for Clarus Ventures, EDev, Sage Therapeutics, Infinity Pharmaceuticals, and Concert Pharmaceuticals. Go to Neurology.org for full disclosures.

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